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WITH POSITIVE NODES AFTER FUNCTIONAL
NECK DISSECTION

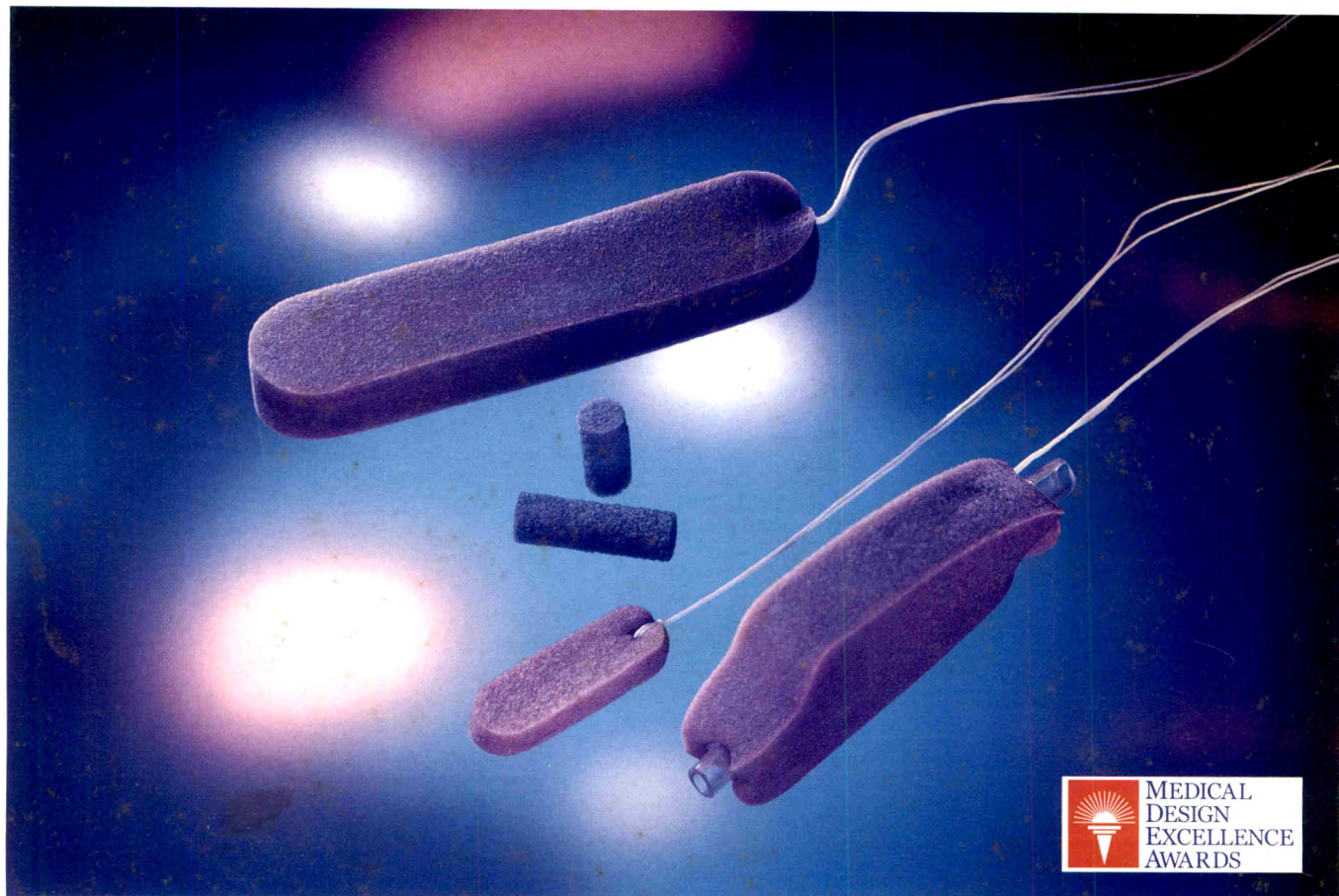


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EXPERIENCE WITH PERCUTANEOUS DILATIONAL TRACHEOSTOMY

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Percutaneous dilational tracheostomy (PDT) has gained popularity among critical care specialists in the past 10 years. The initial studies in our specialty resulted in essentially banning the procedure as a dangerous substitute for standard operative tracheostomy. Despite this action, more than 1,100 cases of percutaneous tracheostomy have been reported with details on complications. We reviewed all published data and studied 311 patients of our own. A prospective study was performed in 3 groups of patients: 1) 50 patients scheduled for PDT performed in the operating room by a head and neck surgeon (group 1); 2) 50 patients who underwent standard operative tracheostomy performed by the same surgeon (group 2); and 3) 211 patients who underwent bedside PDT by critical care physicians (group 3). The intraoperative complication rates were 0% in group 1, 2% in group 2, and 4% in group 3; the postoperative complication rates were 13%, 4%, and 12%, respectively. There were 2 deaths in group 3, and none in groups 1 or 2. The statistically significant differences among the groups were the superiority of group 1 over group 3 in intraoperative complications, as well as the lower postoperative complication rate of the standard tracheostomy group. These results show that PDT can be performed with acceptable morbidity rates in relation to published complication rates of standard tracheostomy, but it has no advantage over standard tracheostomy with respect to postoperative morbidity. When they are performed by a head and neck surgeon, the morbidity associated with both standard and percutaneous tracheostomies can be reduced.

KEY WORDS — airway management, percutaneous tracheostomy, tracheostomy complications.

INTRODUCTION

The standard surgical tracheostomy described by Chevalier Jackson¹ in 1909 has long been the procedure of choice for long-term airway management. Modifications of tracheostomy have sought to decrease the morbidity associated with the procedure. The rate of complications of standard tracheostomy, such as bleeding, infection, and pneumothorax, has ranged widely, from 2% to 66%, with the higher rates occurring in earlier series.²⁻⁷ This discrepancy probably reflects variations in surgical skills, patient characteristics, monitoring, and technique that occurred over time.

Percutaneous tracheostomy was introduced in 1955⁸ and then further developed by Toye and Weinstein,⁹ influenced by the Seldinger technique, in 1969. In 1985, Ciaglia et al¹⁰ originated the technique known as percutaneous dilational tracheostomy (PDT). The procedure is designed to be simply and rapidly performed in a monitored setting such as the intensive care unit (ICU). In addition to decreased morbidity, the potential advantages of PDT include reductions

in cost and surgical time that are realized when the procedure is performed at the bedside.

Since its introduction, PDT has gained widespread use in the ICU by critical care physicians. The immediate popularity of PDT resulted in complication rates as high as 58%,¹¹⁻¹⁵ with paratracheal insertion, severe bleeding, and death more common in the early studies. These initial results contributed to doubts regarding the safety and relative advantages of the procedure.

Although previous studies have compared PDT with standard tracheostomy (ST),¹⁵⁻¹⁷ the procedures were not performed by the same physician. Our objective was to compare the results of PDT and ST when performed by a single head and neck surgeon with the results of PDT routinely performed by a non-surgically trained intensivist.

MATERIALS AND METHODS

Study Population. We performed a prospective study of consecutive adult patients who underwent elective tracheostomy for long-term airway manage-

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ment during a 2-year period at Illinois Masonic Medical Center in Chicago, Illinois. All procedures were performed in the operating room by a single head and neck surgeon (M.F.) who was experienced in both PDT and ST. All patients were intubated before the procedure. By study design, the first 50 patients with an indication for tracheostomy were assigned to undergo PDT and constituted group 1. Group 2 consisted of the next 50 patients, who were assigned to undergo ST.

Group 3 consisted of 211 consecutive adult patients who underwent PDT at Cook County Hospital and Provident Hospital in Chicago over a 3-year period. All patients were intubated before the procedure. The procedures were performed in an ICU by a critical care specialist or by a critical care fellow under the specialist's direct supervision.

In both PDT groups, significant anatomic abnormalities, such as thyromegaly or distortion of the tracheal region, were considered contraindications to the procedure. Patients with these abnormalities were excluded from the PDT groups. In group 1, if clear anatomic landmarks could not be identified, the patient was reassigned to group 2.

The 3 groups were compared with respect to intraoperative and postoperative complication rates.

Techniques. For PDT procedures in groups 1 and 3, the Cook percutaneous tracheostomy introducer set (Cook Critical Care, Bloomington, Ind) was used. Either general anesthesia or local anesthesia with intravenous sedation was used to control pain and level of consciousness. Patients were given 100% oxygen. The endotracheal tube was repositioned above the proposed site of tracheostomy.

A 22-gauge needle was introduced into the trachea through the first or second tracheal interspace. After aspiration of air to confirm placement, 3 to 5 mL of 1% lidocaine hydrochloride was injected into the tracheal lumen. During the procedure, the endotracheal tube was rotated as necessary to ensure that the cuff was not impaled. A 15-gauge needle with an outer Teflon sheath was then introduced into the trachea. After the needle was removed, a J-tipped guide wire was threaded through the Teflon sheath (see Figure, A). An 11F punch dilator was inserted into a 1-cm vertical midline incision made at the skin puncture site. An 8F clear plastic guiding catheter was placed over the guide wire to increase the wire's stiffness and facilitate dilator insertion over the wire (see Figure, B). The tract was progressively enlarged with a series of dilators to allow placement of the tracheostomy tube (see Figure, C,D).

The STs in group 2 were performed as previously

described.¹⁸ In brief, the neck was hyperextended, unless there was a concurrent cervical spine injury. A 3- to 4-cm horizontal incision was made through the skin and platysma. A vertical midline incision through the fascia permitted lateral retraction of the strap muscles. The third tracheal ring was then identified. If found overlying the intended tracheal ring, the thyroid isthmus was bluntly dissected off the trachea and retracted upward after cauterization of the inferior thyroid vein. A tracheal hook was inserted under the cricoid cartilage to stabilize the trachea and pull it up into the field. A portion of the third tracheal ring was excised to create the window for a No. 6 Shiley nonfenestrated, low-pressure cuffed tracheostomy tube. Hemostasis was obtained before insertion of the tube.

We compared the 3 groups with regard to the indication for tracheostomy, as well as the type and frequency of perioperative complications. A 2-sided Fisher's exact test was used for statistical comparison.

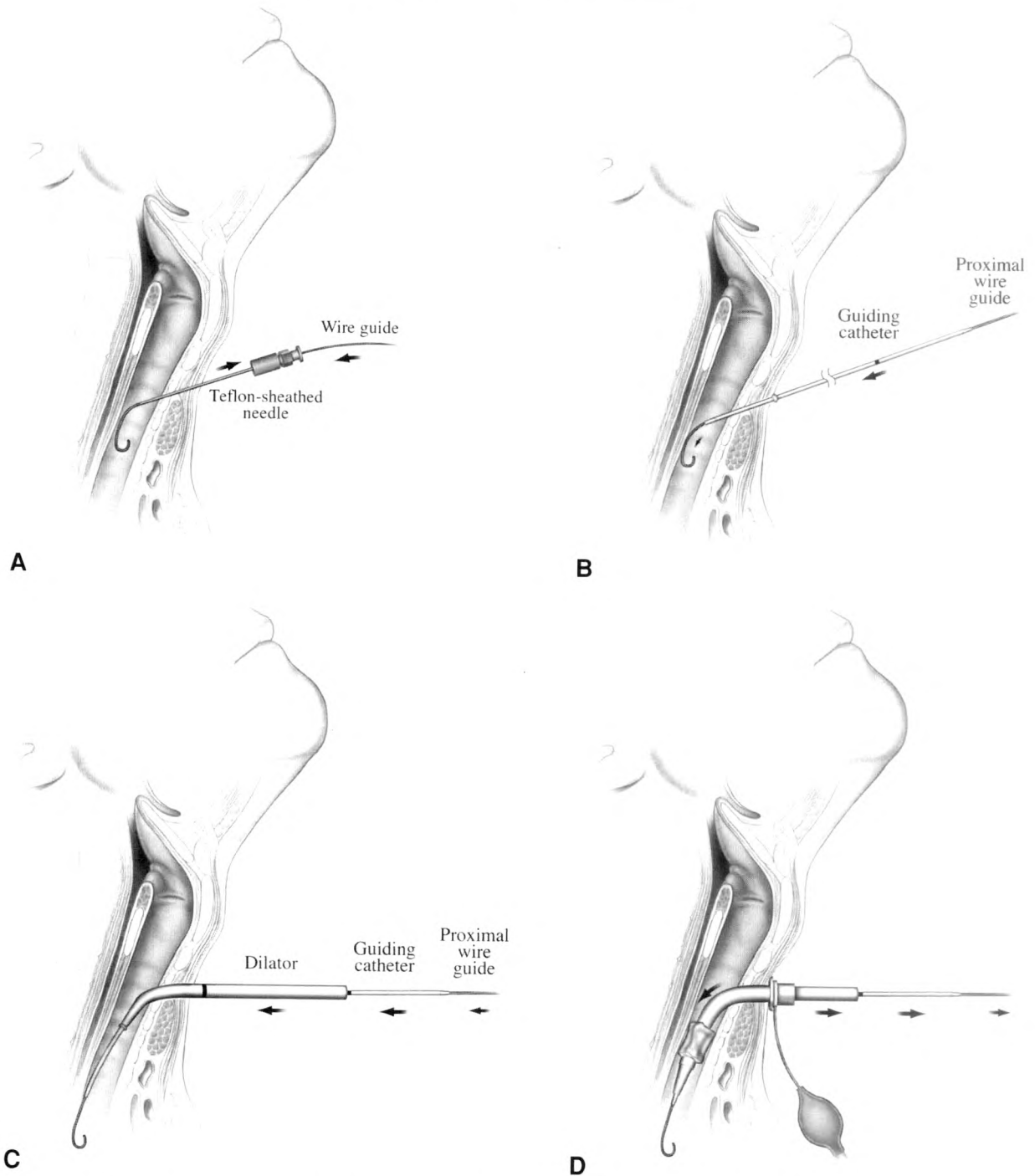
All perioperative complications were recorded. Intraoperative complications such as hypotension, oxygen desaturation, paratracheal insertion, bleeding, and loss of the airway for more than 20 seconds were noted. The postoperative complications included bleeding, subcutaneous emphysema, pneumothorax, accidental decannulation, and stomal infection.

Hypotension was defined as a systolic blood pressure of less than 90 mm Hg. Hypoxia was defined as oxygen saturation of less than 90%. Bleeding was classified as minor (25 to 100 mL), moderate (100 to 250 mL), or severe (>250 mL). Stomal infection was considered present when there was purulent drainage from the site with more than 1 cm of surrounding erythema and induration.

RESULTS

Groups 1 and 2 were comparable with respect to indications for tracheostomy. These included prolonged ventilator dependence, resection of head and neck carcinoma, and airway protection. In all but 1 of the patients with cancer, there was no involvement of the trachea, subglottic larynx, thyroid, or soft tissues of the anterior part of the neck. Of the 50 patients initially assigned to group 1, 11 were reassigned to the ST group because of abnormal cervical anatomy.

In group 3, which contained 250 patients, the reasons for tracheostomy included prolonged intubation, airway protection, and pulmonary toilet. Thirty-nine of these patients were disqualified because of abnormal anatomy, leaving 211 patients who underwent



Procedure of percutaneous dilational tracheostomy. A) J-tipped wire guide inside tracheal lumen after having been threaded through Teflon sheath. B) Guiding catheter with wire guide in position. C) Dilator and wire guide inside tracheal lumen. D) Tracheostomy tube in position before removal of wire guide and guiding catheter.

PDT. Two patients had previously undergone tracheostomy.

The complication rates in the 3 groups are shown in Table 1. No intraoperative complications occurred in the 39 patients in group 1 who underwent PDT. Postoperative complications occurred in 5 patients (13%); minor bleeding occurred in 3 patients (8%) and was controlled with packing, and subcutaneous

emphysema developed in 2 patients (5%) and resolved spontaneously. There were no deaths related to the procedure.

In the ST group ($n = 50$), the intraoperative complications were limited to 1 case of transient hypotension (2%). Two patients (4%) had moderate postoperative bleeding. One of these patients had chronic renal failure and coagulopathy; the bleeding was

TABLE 1. COMPLICATION RATES FOR PDT AND ST GROUPS

Complications	Group 1	Group 2	Group 3
Intraoperative	0*	1 (2%)	8 (4%)
Postoperative	5 (13%)	2 (4%)†	25 (12%)
Group 1 — percutaneous dilational tracheostomy performed by a single head and neck surgeon (n = 39); group 2 — standard tracheostomy performed by same surgeon as group 1 (n = 50); group 3 — percutaneous dilational tracheostomy performed by a non-surgeon (n = 211).			
*Statistically significantly superior to group 3 (p = .039 by Fisher's exact <i>t</i> -test).			
†No statistically significant difference between group 2 and other groups (p = .158).			

stopped with packing and transfusion of platelets. The second patient had a locally invasive carcinoma and required postoperative neck exploration for control. There were no deaths related to the procedure.

For the 211 patients in group 3, the intraoperative complication rate was 4%; transient oxygen desaturation occurred in 4 patients (2%), transient hypotension in 3 (1.5%), and paratracheal insertion in 1 (0.5%). One of the cases of hypoxia occurred as a result of extubation during the procedure. The postoperative complication rate was 12%; bleeding occurred in 19 patients (9%), stomal infection in 3 (1.5%), subcutaneous emphysema in 2 (1%), and tracheostomy tube dislodgment in 1 (0.5%). There was minor to moderate bleeding controlled with packing in 16 patients, 5 of whom required transfusions of packed red blood cells. Two of the 3 patients who had severe bleeding died. In 1 patient, a trachea-innominate artery fistula was presumed to have developed 6 days after PDT. In the other case of massive hemoptysis, no cause was clearly demonstrated on postmortem examination. The third patient was found to have a benign exophytic lesion above the tracheostomy. One case of stomal infection contributed to systemic sepsis 22 days after the procedure. All cases of subcutaneous emphysema resolved spontaneously. Two patient deaths occurred within a 6-day postoperative period. Table 2 shows the major and minor complications in each group.

A statistical comparison of the complication rates between the groups, using a 2-sided Fisher's exact test, yielded 1 significant difference between groups: the intraoperative complication rate in group 2 was significantly lower than that in group 3 (p = .039). The postoperative complication rates for the ST and PDT groups were comparable (p = .158). However, group 3 experienced major perioperative complications not seen in the other 2 groups. The only deaths occurred in group 3.

DISCUSSION

Both ST and PDT are associated with known com-

TABLE 2. PERIOPERATIVE COMPLICATIONS

Complications	Group 1	Group 2	Group 3
Major			
Paratracheal insertion	0	0	1
Severe bleeding	0	0	3
Death	0	0	2
Minor			
Transient hypotension	0	1	3
Transient hypoxia	0	0	4
Subcutaneous emphysema	2	0	2
Minor to moderate bleeding	3	2	16
Tube dislodgment	0	0	1
Stomal infection	0	0	3
Total	5 (13%)	3 (6%)	35 (17%)

plications, which include local bleeding, pneumothorax, and infection. Tracheal stenosis has also been reported as a late complication. Although open tracheostomy remains the standard for long-term airway management, PDT has rapidly gained wider use because of its potential economic and logistic advantages.

The initial reports in the otolaryngological literature were discouraging, with high complication rates. Wang et al¹⁴ reported their experience with a small group of patients who underwent percutaneous tracheostomy. The authors emphasized the need to identify the ideal patient with optimal cervical anatomy. In patients with these characteristics, PDT is superior to ST in terms of speed and simplicity. However, the authors clearly emphasized the need for thoroughly training physicians to perform the procedure and minimize morbidity. Because of the high complication rate in their study, which included 1 death, the recommendation was that the technique be abandoned.

Two distinct differences exist between this study and our own. First, the Shiley kit used in the study by Wang et al¹⁴ has been discontinued owing to the high complication rate. The Cook kit is the dilational unit most commonly used today. Second, the site of entry into the trachea (midway between the cricoid cartilage and the sternal notch) used in the earlier study is imprecise and appears to be lower than the one used in our procedures. Low in the neck, the trachea is deeper from the point of entry during PDT. Thus, the likelihood of bleeding or creation of a false passage is increased. As more experience is accumulated, the appropriate applications and optimal technique are becoming better defined. In more recent studies, including our own, the complication rates have been acceptable and comparable with those of ST.^{15,16,19} In addition to a shorter procedure time, the other advantages of PDT that have been cited are decreased costs for patient transport,²⁰ avoidance of

complications associated with transport from the ICU to the operating room,²¹ and less time between the decision for and the performance of tracheostomy.

Several potential disadvantages of PDT need to be addressed. First is the possibility of accidental dislodgment of the tracheostomy tube after the procedure. In that event, it may be difficult to find the opening into the tracheal lumen. In contrast, with the ST, the tracheal window can be identified by a fingertip technique²² or by using stay sutures left in position at the time of the original procedure. In our study, no instances of dislodgment occurred in groups 1 and 2. In group 3, the single episode of accidental decannulation was resolved uneventfully with immediate reinsertion of the tube.

Second, because PDT is performed in a "blind technique," paratracheal insertion, bleeding, and injury to the posterior tracheal wall are recognized possible complications. The use of endoscopic guidance with PDT has been advocated to avoid injury and ensure correct tracheostomy position.²³⁻²⁵ In a prospective study of 76 patients by Berrouscho et al,²⁵ the perioperative complication rates of PDT groups with and without bronchoscopy were similar (6% and 7%). However, the more severe complications (massive intratracheal bleeding, pneumothorax, and tracheal injury) occurred in the group that underwent PDT without endoscopic guidance. There was 1 death in each group. The endoscopy is relatively simple to perform without impairing access during the procedure.

In our study, endoscopic guidance was not used. No intraoperative complications occurred in the PDT-surgeon group, and no major complications or deaths occurred in the surgeon groups. The lower intraoperative complication rate in group 1 and the larger number of major complications in group 3 may indicate the more judicious selection of patients for PDT by the head and neck surgeon, as well as interoperator variability. Positioning of the patient was not a determining factor, because during the PDTs performed in the operating room or in the ICU, the patients remained stabilized in their beds and were not transferred to an operating room table.

Certain contraindications to the use of the procedure have been identified, such as a large thyroid goi-

ter or other neck mass, marked obesity, coagulopathy, inadequate access to the trachea, previous cardiac procedures, and neck traumas, including burns.

Also, PDT has traditionally not been recommended in children.¹¹ However, Toursarkissian et al²⁶ reported favorable results in the use of PDT in children and teenagers. In that study, 11 children 10 to 20 years of age (average, 16 years) underwent PDT for prolonged ventilator support or pulmonary toilet access with the Cook kit. The average endolaryngeal intubation period was 12 days. Nine of the patients were decannulated with evidence of tracheal stenosis after an average follow-up of 39 weeks (range, 4 to 73 weeks). Stenosis was evaluated on the basis of symptoms alone. Aside from this sole review, further examination of the effects of PDT in children should be conducted before the traditional recommendation is changed.

The PDT method compares favorably with the standard technique, but ST has wider applicability, as 20% of our patients in group 2 were moved to that group because of anatomic abnormalities. The key to safe and effective airway management with PDT is appropriate patient selection. A surgeon skilled in both techniques would enjoy a significant advantage, particularly because the use of PDT in the ICU has been well established. The PDT method, however, shows a major disadvantage in the study. No deaths occurred in groups 1 and 2 (head and neck surgeon groups), compared with 2 perioperative deaths in group 3. Morbidity and mortality rates were not studied for tracheostomy procedures performed at the same institution in which the group 3 patients were treated (a city teaching hospital), but morbidity and mortality rates of ST have been previously published.^{15,16,19}

CONCLUSION

Percutaneous dilational tracheostomy should be recognized as a valid technique in adult airway management. Our study indicates that ST or PDT performed by a surgeon results in lower perioperative morbidity and mortality rates when compared with PDT performed by a critical care specialist. Although PDT performed by a critical care specialist has complication rates comparable with published rates for ST, PDT was associated with postoperative death, which is not frequently reported with ST.

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PREVENTION OF ACCIDENTAL CHILDHOOD STRANGULATION

A CLINICAL STUDY

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Accidental strangulation is a preventable problem, and there is limited scientific understanding of its mechanism in children. If the amount of external pressure that occludes the airway can be determined, design changes may be made to allow for production of household objects that would break apart at safe pressure levels. A force gauge was applied to the suprahyoid region in 90 children under standardized anesthesia. Three blinded observers performed the study. The anesthesiologist maintained the airway and used a stethoscope to auscultate for breath sounds and monitor the CO₂ curves to evaluate obstruction. The recorder noted the numbers from the gauge. A single observer applied the force gauge. Age was the most significant variable in occluding the airway. Obstruction appears to occur at the level of the larynx. Increased knowledge regarding the external pressure required for airway occlusion would allow for the design and manufacture of products with a reduced potential for accidental strangulation.

KEY WORDS — accident, airway obstruction, injury, neck, prevention.

INTRODUCTION

The leading cause of death in children is accidental trauma. Asphyxia was the most common cause of infant deaths reported by the National Center for Health Statistics in 1997 (Fig 1).¹ The annual incidence of unintentional pediatric asphyxia deaths is 11.0 per 100,000 infants in the United States. Ropes or cords were involved in 24% of asphyxias in the United States (choking episodes involved 9% of asphyxias)² and in 17% of asphyxias in Wales and England.³ The incidence of accidental fatal asphyxia has not decreased significantly since 1962, despite US federal regulation changes. In fact, the US National Center for Health Statistics reported that the incidence of asphyxia in infants in 1995 was 10% higher than that from 1985.¹ There is a surprising lack of clinical research on childhood accident prevention. A common scenario in the United States involves window-covering cords in which infants become entangled while sleeping and from which toddlers become suspended while playing on or jumping from furniture.

Hanging is caused by constriction of the neck as a result of suspension in such a manner that the weight of all or a part of the body pulls on the ligature.⁴ These forces constrict the airway in a vector directed superior and posterior (Fig 2). Suspension occurs

above the larynx but below the angle of the jaw, as noted in 80% of adult hangings.⁴ Jaw projection prevents superior displacement of the ligature.

There is very little information regarding the internal mechanisms that result in this unfortunate event. Airway obstruction in hanging is currently believed to occur as the base of the tongue is pushed against the posterior wall and the epiglottis folds over the larynx.⁴ The arteries and veins have a major role in strangulation. Adult autopsy studies performed by Brouardel⁵ in France in the 19th century showed that the amount of mass needed to occlude the carotid

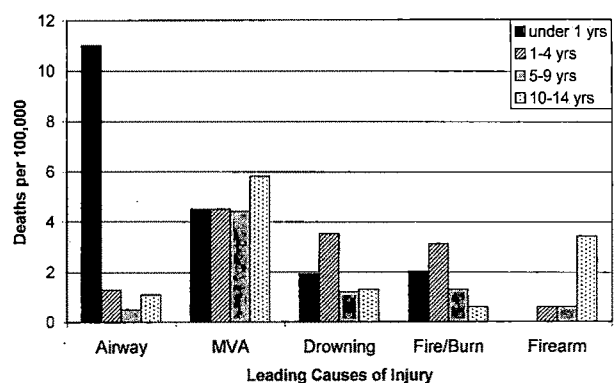


Fig 1. Death rates for leading causes of injury among children under 15 years of age in United States in 1995. (Data from National Center for Health Statistics.¹)

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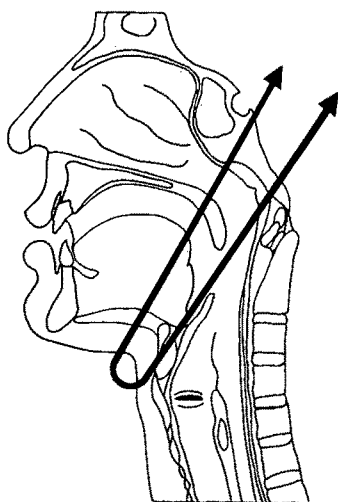


Fig 2. Sagittal view of head and neck with representative loop demonstrating location of suspension hanging. (Modified with permission from McGee JP, Vender JS. Nonintubation management of the airway: mask ventilation. In: Benumof JL, ed. Airway management: principles and practice. St Louis, Mo: Mosby-Year Book, 1995:228-54.)

artery was 5 kg, the internal jugular vein 2 kg, and the trachea 15 kg.

In adults, accidental strangulation or hanging is far less common than homicide or suicide, which usually involves complete suspension. Judicial hanging involves a drop at least equal to the height of the person to result in an odontoid fracture.

The most common scenario in young children is partial hanging. Partial hanging occurs when a portion of the body is supported (ie, kneeling or standing). In partial hanging, tension applied to the neck may occlude the airway but not the artery, resulting in asphyxia. Regardless of whether it is partial or full suspension, the forces are similar on the neck.

Accidental strangulation is a preventable problem with limited scientific understanding in children. Where does obstruction occur? How much force does it take to significantly obstruct the airway? If this information was known, many of these events could be prevented by designing products to reduce the risk of strangulation.

As part of a study regarding maintenance of the airway in small children, observations were made that led to this study of suspension. Our present study was designed to evaluate the amount of force applied to the hyoid region of the neck needed to occlude the airway. Additional factors of weight, age, and sex were evaluated for any correlation. Tooth eruption, tonsil size, and placement of an oral airway were evaluated to determine the internal site of obstruction (hanging) and were verified by flexible endoscopy.

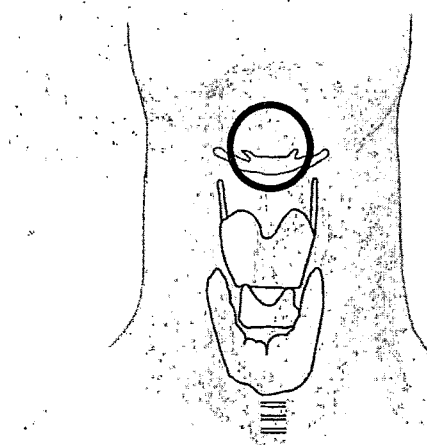


Fig 3. Demonstration of position of force gauge on neck with landmarks for reference. (Modified with permission from Silver CE. Surgical anatomy. In: Silver CE, Ferlito A, eds. Surgery for cancer of the larynx and related structures. Philadelphia, Pa: WB Saunders, 1996:13-26.)

MATERIALS AND METHODS

This study was approved by the institutional review board at The University of Colorado Health Sciences Center in Denver, Colo. At the Children's Hospital in Denver, the study was performed after obtaining informed consent from the legal guardian. The study occurred in the operating room at the beginning of elective surgical procedures. Patients from the pediatric otolaryngology, dental, urology, and ophthalmology services were enrolled from July through October 1997. Excluded were patients with a history of sleep apnea; patients scheduled for tonsillectomy or adenoidectomy; patients with asthma or reactive airway disease, craniofacial abnormalities, or variance from neutral position; and patients with abnormal airways (eg, tracheomalacia) as determined by the surgeon or anesthesiologist.

Variables of age, weight, sex, tonsil size, and primary tooth eruption were noted. Tonsil size was rated on a scale of 1+ to 4+. Presence of primary teeth, which may increase the size of the airway by jaw displacement, was scored from 0 to 3: 0, no teeth; 1, incisors only; 2, early erupted molars or molars worn to the gingiva in the case of dental patients who were undergoing restorations; and 3, fully erupted molars.

A force transducer (Omega Corp, Stamford, Conn; 0- to 250-lb load cell) was specifically constructed for this purpose. Preliminary evaluations used a larger-diameter force device that was subsequently modified to a round device approximately the diameter of a US penny. Preliminary evaluations used a drop in the pulse oximetry levels to determine obstruction. This was not reliable and took too long to be applicable to a brief study period of 5 seconds of obstruction.

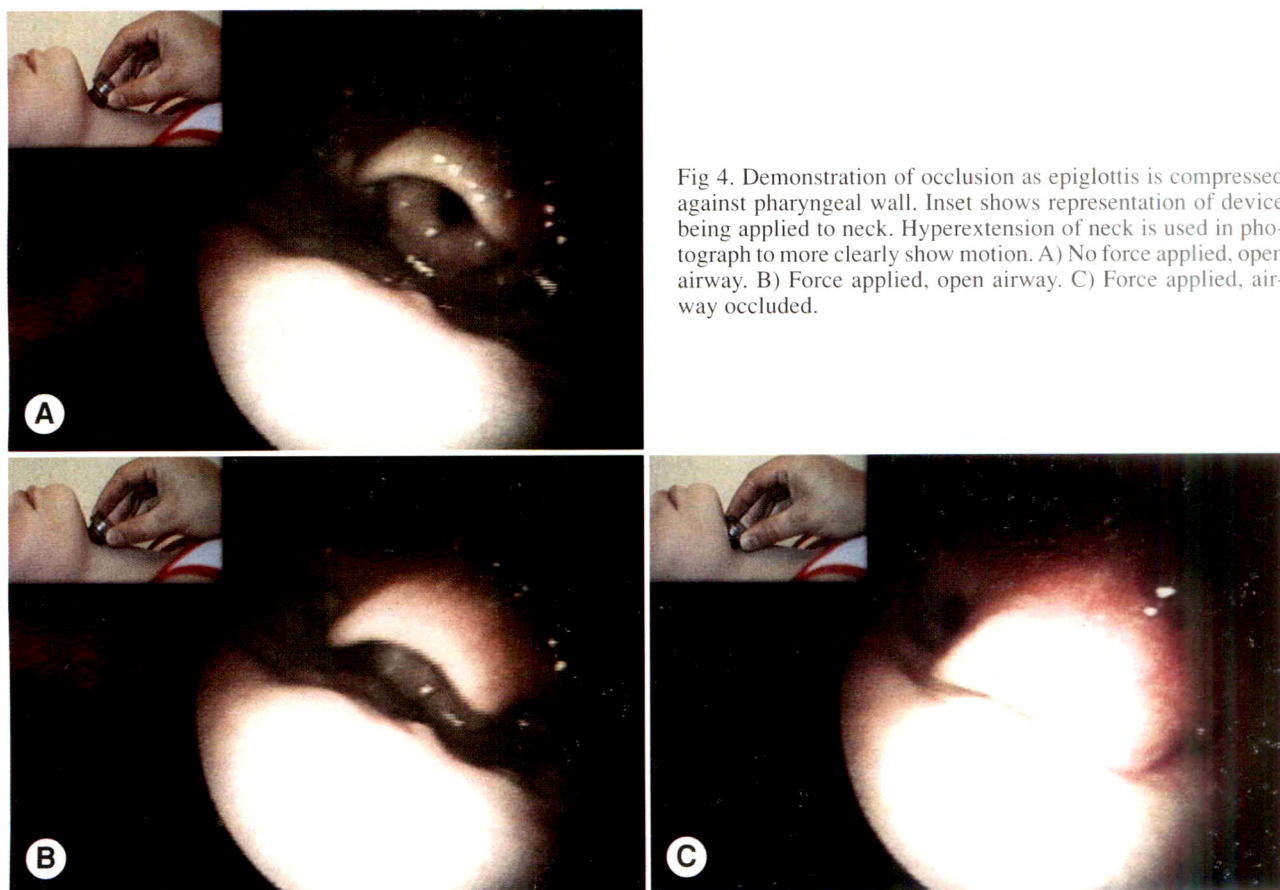


Fig 4. Demonstration of occlusion as epiglottis is compressed against pharyngeal wall. Inset shows representation of device being applied to neck. Hyperextension of neck is used in photograph to more clearly show motion. A) No force applied, open airway. B) Force applied, open airway. C) Force applied, airway occluded.

tion. Using the anesthesiologist's tools of auscultating and observing the cessation of CO₂ output on the monitor was more appropriate for these brief episodes of obstruction. Obstruction was quantified as the absence of sound with respiratory effort. Attempts were made to quantify the obstruction on the basis of auscultation, but were difficult to reproduce among 13 different pediatric anesthesiologists.

A round force gauge 19.5 mm in diameter was applied to an area in the midline centered millimeters above the hyoid bone in a posterior-superior vector (Fig 3). Before each patient's application, the gauge was zeroed and calibrated to a known weight in pounds. The patients received an inhalation induction with halothane, nitrous oxide, and oxygen. Patients were started in the neutral position, and any variance led to exclusion. The neutral position was determined by approximation of the patient's head lying perpendicular to the Frankfort horizontal plane.

This study situation is an artificial situation for suspension. Under general anesthesia, the upper airway muscles relax and are known to be a site of obstruction requiring airway maneuvers. For a child in respiratory distress and losing consciousness, however, the situation may not be that different from general anesthesia. Additionally, 10 children were ex-

cluded because they could not tolerate the neutral position and required airway maneuvers. The neutral position can be subtle and lead to variances in data.

Another tool, the Guedel oral airway, was used to help evaluate the obstruction. Selection of the size of the oral airway was the anesthesiologist's choice. The oral airway can paradoxically contribute to obstruction if it is inappropriate in size or placement. Placement of an oral airway that is too small or too far anterior can cause the tongue to be pushed posteriorly. Placement of the oral airway too far posterior can push against the vallecula or the epiglottis, causing narrowing of the laryngeal vestibule.

Once the patient was well oxygenated and at least at the third level of anesthesia as determined by the anesthesiologist, permission to proceed was obtained and the study was performed. Three observers were involved to eliminate bias. The anesthesiologist maintained the airway and used a stethoscope to listen for breath sounds to decide when the airway was 100% obstructed and informed the recorder. Force was applied for 3 separate 5-second investigations. A single observer applied force to the force gauge, blinded to the obstruction and to the numbers on the pressure gauge. The recorder wrote the numbers from the strain

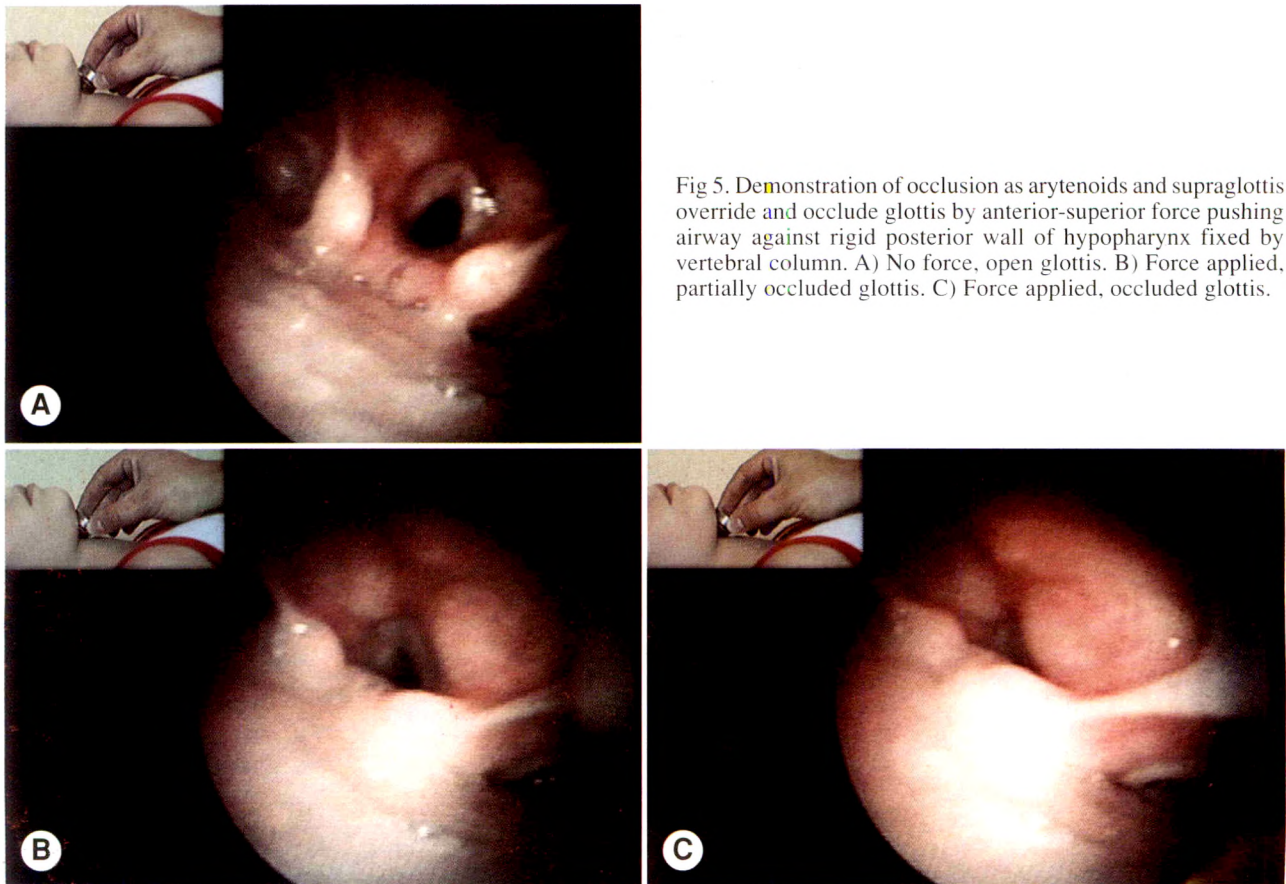


Fig 5. Demonstration of occlusion as arytenoids and supraglottis override and occlude glottis by anterior-superior force pushing airway against rigid posterior wall of hypopharynx fixed by vertebral column. A) No force, open glottis. B) Force applied, partially occluded glottis. C) Force applied, occluded glottis.

gauge when instructed by the anesthesiologist that the airway was obstructed. Confirmation of occlusion was made by observing the absence of CO₂ curves, sampled at the 90° elbow of the pediatric anesthesia circuit of the mask with an Ohmeda 5240 Respiratory Gas Monitor (Ohmeda, Louisville, Colo). Once occlusion was confirmed, the force was removed (Figs 4 and 5). Afterward, the oral airway was selected and placed by the anesthesiologist, and 3 additional applications were performed.

RESULTS

Ninety ASA I and II (American Society of Anesthesiologists physical status classification) children

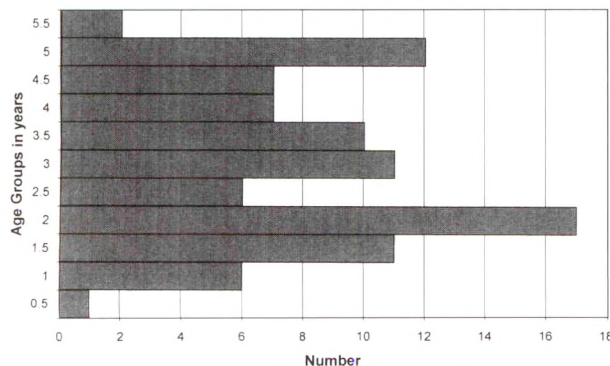


Fig 6. Number of children enrolled per study group based on age.

5 months to 5¹/₂ years of age participated in the study. The population included 57 boys (63%) and 34 girls (37%). For statistical purposes, the children were grouped according to age. There was 1 child 0 to 0.5 years, 6 children 0.51 to 1.0 years, 11 children 1.01 to 1.5 years, 17 children 1.51 to 2.0 years, 6 children 2.01 to 2.5 years, 11 children 2.51 to 3.0 years, 10 children 3.01 to 3.5 years, 7 children 3.51 to 4.0 years, 7 children 4.01 to 4.5 years, 12 children 4.51 to 5.0 years, and 2 children 5.01 to 5.5 years. Figure 6 demonstrates the distribution of the children enrolled by age group. Medical histories included 5 children born prematurely, 1 tracheoesophageal fistula repair, 1 set of twins, 1 ventricular-peritoneal shunt, 1 pyloroplasty, and 1 repaired cardiac ventricular septal defect. There were no significant complications and, specifically, no episodes of laryngospasm. During the testing, there was 1 episode of tachypnea and erratic breathing lasting 60 seconds that resolved after repositioning and placement of an oral airway. Another patient had an episode of bradycardia that immediately resolved when the pressure was released. After the study, all surgical procedures were performed as planned.

The 3 forces in each child were averaged before analysis — the range of forces was 0.9 to 21 N (0.2 to 4.6 lb). The mean was 7.1 N (1.6 lb), with a stan-

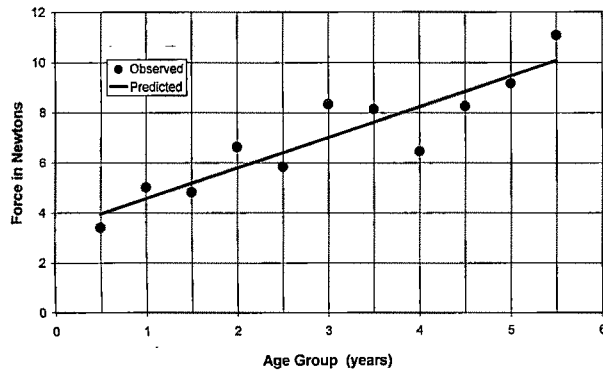


Fig 7. Graph of average force in newtons across age groups. Best fit line, $y = 1.2091x + 3.3455$; $r^2 = 0.8289$.

dard of error of 0.08 N and a standard deviation of 3.5 N (0.78 lb). A linear graph expressing age versus force is shown in Fig 7. Sex, weight, and tonsil size were not found to correlate with the amount of pressure. After adding the oral airway, the mean became 7.6 N (1.7 lb) with a standard of error of 0.81 N. Figure 8 displays the force required with and without an oral airway. The difference between data obtained with and without the oral airway was not significant for the population studied.

DISCUSSION

The pediatric airway rapidly approaches adult anatomy in the first years of life, yet there are many differences between the airways of infants and adults. Infants have large and heavy heads, the tongue is large, and the larynx is more cephalad. The glottic opening is at the level of the third or fourth cervical spine interspace in full-term infants and descends to the level of the fifth cervical body. Other changes that occur include tooth eruption, with its effect of mandible displacement, especially by the molars that begin to erupt around the first year. The mandible has muscular and fibrous attachments that with anterior and inferior displacement open the airway. This is the mechanism by which intraoral devices help decrease airway collapse in obstructive sleep apnea.

The airway of infants is anatomically vulnerable at the oropharynx between the soft palate and the skull, as described by Tonkin⁶ in her hypothesis of sudden infant death syndrome. She found that the mandible is almost horizontal, with a short ramus, and has a soft, cartilaginous mandibular head. The mandible is also more mobile than in adults and can easily be retrognathically displaced in the prone position. This carries the tongue backward and upward against the soft palate, causing occlusion of the airway.

The lack of correlation with tonsil size, tooth eruption, or placement of an oral airway in this study sup-

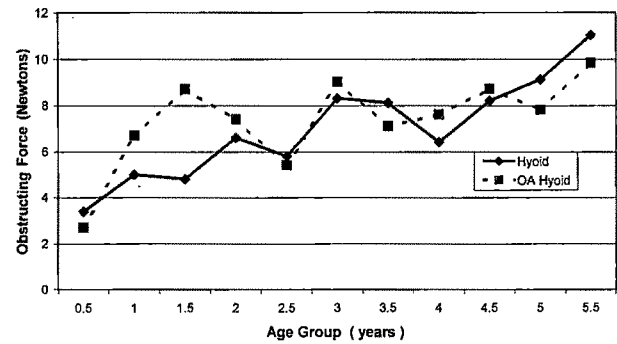


Fig 8. Comparison of obstructing forces and age in data obtained with ("OA hyoid") and without ("hyoid") oral airway. Data are not significantly different with application of oral airway.

ports the larynx as the site of obstruction. Previously, we reported fiberoptic observations of 8 of our patients and demonstrated that suprahyoid pressure caused the hyoid bone and the thyroid cartilage to move superior and posterior.⁷ This caused occlusion at 2 points: the epiglottis was compressed against the pharyngeal wall, and the arytenoids and supraglottis overrode and occluded the glottis by the anterior-superior force pushing the airway against the rigid posterior wall of the hypopharynx fixed by the vertebral column. After a near-hanging, children's airways are more vulnerable than those of adults to delayed edema because of the small diameter. Finally, the young child is unaware of the situation, is unable to realize the danger, and is relatively unable to escape.

The mean force we found needed to occlude the airway of 7.1 N (1.6 lb) demonstrates the ease of airway occlusion in children. The measurement at the fifth percentile (2.2 N [0.5 lb]) is used for injury prevention. This limit is important in designing and evaluating consumer goods for injury prevention.

Events involving the cords of window blinds are one of the situations of unintentional mechanical asphyxia for which this information could be generalized to remove the hazard. Window-blind cords have caused a significant amount of injury in the state of Colorado (unpublished data). Since January 1997, the voluntary standard as proposed by the Consumer Product Safety Commission has been to produce miniblinds with 2 cord tassels or a single break-apart tassel. (Modifications of existing blinds are available; one can telephone 1-800-506-4636 to request tassels and tie-down devices free of charge). Despite these efforts, the products are in use in large quantities, and there is a significant delay for products to be replaced to improve safety.⁸ The voluntary change only eliminates a portion of the risk, because long pull cords and slat strings still pose a significant risk to children.

The goal is to have safety built into products. Risk to a child is directly related to the hazard and to exposure (risk = hazard $\times$ exposure). The key is developing effective, easy-to-use, passive, "built-in" safety measures that have a minimal or preferably no effect on cost or product use. Active measures that require modifications of human behavior evoke less compliance than passive environmental measures.⁹ Research is under way on making this information on childhood airways applicable to products with foreseeable use that could result in hanging or strangulation.

CONCLUSION

The amount of pressure needed to occlude the airway is surprisingly low. Age characteristics should

be taken into account to ensure safety under conditions of foreseeable use. Retrospective data have been retrieved from the Colorado State Department of Public Health and Environment and major hospitals over the past 12 years on incidence, clinical course, and outcomes in children 0 to 18 years of age involved in accidental mechanical asphyxia.

Hanging occurs when all or part of the weight of the body causes a ligature to constrict. Our finding no correlation with tonsil size or oral airway application provides information to exclude the tongue, soft palate, and oropharynx as the location of obstruction. Direct observation revealed that obstruction of the airway occurs at the level of the larynx. Accidents may be prevented with improved product design.

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DILATATIONAL VERSUS STANDARD TRACHEOSTOMY: A META-ANALYSIS

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The advent of percutaneous dilatational tracheostomy (PDT) was initially viewed by otolaryngologists with great skepticism. The purpose of this study was to compare the complications of PDT with those of standard tracheostomy (ST) by a meta-analysis of randomized studies. We found that ST had a fivefold higher rate of complications than did PDT, and these complications were often more severe. We conclude that PDT is a safer procedure for elective tracheostomy in carefully selected patients, ie, those with normal-sized necks.

KEY WORDS — dilatational tracheostomy, endoscopic tracheostomy, percutaneous tracheostomy, tracheostomy.

INTRODUCTION

Otolaryngologists have been reluctant or slow to develop the technique of percutaneous dilatational tracheostomy (PDT), largely because of our familiarity with and ease in performing standard tracheostomy (ST) and cricothyroidotomy. For our specialty, PDT appeared to be a potentially hazardous procedure; after the presentation and publication of the University of California–Los Angeles group's adverse experience with a new percutaneous kit,¹ it is not surprising that we did not embrace this technique sooner.

The purpose of this study was to compare the complications of ST and PDT by meta-analysis.

MATERIALS AND METHODS

A Medline search performed up to and including January 31, 1999, retrieved 256 citations. The selection criteria for suitable studies included those that were randomized, were prospective, and compared dilatational tracheostomy (percutaneous tracheostomy) with standard open surgical tracheostomy. Our

reasoning was that those physicians capable of performing both procedures would have no inherent bias favoring one technique over another. The search words used were dilatational tracheostomy, percutaneous tracheostomy, and endoscopic tracheostomy. Two hundred fifteen of the articles were in English, and the remainder were in various other languages.

RESULTS

Only 4 randomized, prospective trials, reporting 212 patients, were found. One hundred three patients were randomized to the PDT group, and 109 to the ST group. No significant differences were found among the individual studies in terms of indications for procedure or demographic data, as shown in Tables 1 and 2.²⁻⁵ Pulmonary diseases, such as pneumonia, respiratory failure, and chronic obstructive pulmonary disease, were the most common indications for tracheostomies, followed by neurologic insults, such as stroke and central nervous system trauma. The third most common indication was cardiovascular disorders, such as heart failure and myocardial

TABLE 1. PATIENT DEMOGRAPHICS

	<i>Hazard et al</i> ²		<i>Crofts et al</i> ³		<i>Friedman et al</i> ⁴		<i>Holdgaard et al</i> ⁵		<i>Totals</i>	
	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>
No. of patients	22	24	25	28	26	27	30	30	103	109
Male/female	12/10	13/11	12/13	19/9	14/12	17/10	24/6	22/8	62/41	71/38
Age (y)	61 ± 19	65 ± 18	59.2 ± 16.4	59.4 ± 18.3	53 ± 20	53 ± 17	54.5 (18-79)	65.5 (18-78)	58	61
Days intubated	7.7 ± 3.9	9.2 ± 3.2	12.5 ± 6.3	10.5 ± 5.0	17.2 ± 7.5	21.3 ± 26.2	6.5	7	11	12
Tracheostomy (d)	16.9 ± 12.9	22.0 ± 10.0	NA	NA	24.5 ± 20.1	18.5 ± 11.8	9	10.8	17	17

PDT — percutaneous dilatational tracheostomy, ST — standard tracheostomy, NA — not available.

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TABLE 2. INDICATIONS FOR SURGERY

	<i>Hazard et al</i> ²		<i>Crofts et al</i> ³		<i>Friedman et al</i> ⁴		<i>Holdgaard et al</i> ⁵		<i>Totals</i>	
	PDT	ST	PDT	ST	PDT	ST	PDT	ST	PDT	ST
Pulmonary (pneumonia, respiratory failure, COPD, etc)	13 (59%)	19 (79%)	4 (16%)	3 (11%)	22 (85%)	22 (81%)	4 (13%)	3 (10%)	43 (42%)	47 (43%)
Cardiovascular (heart failure, MI)	5 (23%)	10 (42%)	3 (12%)	6 (22%)	2 (8%)	2 (7%)	6 (20%)	8 (27%)	16 (16%)	26 (24%)
Systemic disorders (shock, sepsis)	11 (50%)	9 (38%)	0 (0%)	0 (0%)	4 (15%)	2 (7%)	NA	NA	15 (15%)	11 (10%)
Neurologic (stroke, CNS injury)	6 (27%)	2 (8%)	14 (56%)	17 (61%)	NA	NA	12 (40%)	10 (33%)	32 (31%)	29 (27%)
Trauma	5 (23%)	0 (0%)	4 (16%)	1 (4%)	NA	NA	5 (16%)	4 (13%)	14 (14%)	5 (5%)
Gastrointestinal	0 (0%)	0 (0%)	0 (0%)	1 (4%)	NA	NA	2 (7%)	2 (7%)	2 (7%)	3 (3%)

COPD — chronic obstructive pulmonary disease, MI — myocardial infarction, CNS — central nervous system, NA — not available.

infarction.

The 4 studies examined intraoperative differences between the 2 methods of tracheostomy (Table 32-5). Not all the same factors were studied, but distinct trends can be seen. The PDT method was faster (8 minutes, versus 20.9 minutes for the ST group). Additionally, PDT patients experienced a smaller drop in their intraoperative arterial oxygen saturation level (96.8%, versus 93.7%) and had less frequent episodes of minor bleeding.

Postprocedural complications are outlined in Table 4.2-5 A fivefold greater number of postprocedural complications after ST is reported. The incidence of minor bleeding and stomal infection was lower in the PDT group. Three deaths occurred in the ST group, which were all reported in the Friedman et al⁴ paper; 2 of the 3 deaths occurred after accidental decannulation in which attempted reinsertion and reintubation failed. Despite retention sutures around the tracheostomy tube in an extremely obese neck, the first decannulation occurred while the patient was being turned within the first 2 hours of arrival in the intensive care unit. The second decannulation occurred 1 week after ST in a patient with a stomal wound infection that made reinsertion of the tube difficult. The third death occurred 6 weeks after surgery, apparently from a massive hemorrhage resulting from a tracheoinnominate fistula. The ST group had 3 episodes of pneumothorax, compared with only 1 occurrence in the PDT group, and 2 episodes of documented aspiration, versus 1 in the PDT group.

Table 5 shows the results for decannulated patients as reported by Hazard et al² and Friedman et al.⁴ The PDT group demonstrated a small trend toward a great-

er number of patients who were successfully decannulated. Decannulation occurred within fewer days, and this group also experienced a higher survival rate.

DISCUSSION

Standard tracheostomy dates back thousands of years, as historical references recount creating an opening in the trachea; however, this procedure was condemned and considered dangerous and irresponsible until the early-to-middle 19th century. In 1833, Trousseau reported his series of 200 patients who underwent tracheostomy for diphtheria, but it was not until 1909, when Chevalier Jackson demonstrated the relative safety and efficacy of ST, that the surgical community embraced it.⁶

Percutaneous dilatational tracheostomy was developed shortly after Seldinger's important description of needle replacement over a guide wire in arterial catheterization. In 1955, Sheldon et al⁷ first attempted percutaneous tracheostomy with a slotted needle and a cutting trocar used to create an opening into the trachea. The technique was regarded with great skepticism, as multiple deaths occurred. Since that time, 4 different techniques of percutaneous tracheostomy have been reported. In 1969, the Toye and Weinstein⁸ method of using a single tapered dilator with a recessed cutting blade was reported; in 1985, Ciaglia et al⁹ described the PDT method via the Seldinger approach; in 1989, Schachner et al¹⁰ developed the Rapitrac method of forcibly advancing a beveled metal conus over a wire; and in 1990, Griggs et al¹¹ presented their guide wire dilating forceps method. Except for the PDT method proposed by Ciaglia et al, the various percutaneous methods have not gained in popularity, mainly because of their difficulty of

TABLE 3. INTRAOPERATIVE COMPLICATIONS

	<i>Hazard et al</i> ²		<i>Crofts et al</i> ³		<i>Friedman et al</i> ⁴		<i>Holdgaard et al</i> ⁵		<i>Totals</i>	
	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>
No. of procedures	24	24	25	28	26	27	30	30	103	109
Procedure duration (min)	4.3 ± 2.2*	13.5 ± 7.3	NA	NA	8.2 ± 4.9†	33.9 ± 14.0	11.5 (7-24)§	15.5 (5-47)	8	20.9
Lowest SaO ₂ (%)	96 ± 5	92 ± 11	NA	NA	NA	NA	97.6 ± 3.1	95.4 ± 3.9	96.8	93.7
Major bleed (ligatures needed in ST or electrocautery in PDT)							0	2		
Minor bleed (pressure)					3 (12%)	3 (11%)	6 (20%)	24 (80%)	9 (9%)	27 (25%)
Cuff puncture							5	0		
Paratracheal insertion					1 (4%)	0				
Resistance to insertion of tracheostomy tube							8	0		
Transient hypotension (SBP of <90)					4 (15%)	3 (11%)				
Transient hypoxia (<90% oxygen saturation)					0	3 (11%)				
Loss of airway (>20 s)					0	1 (4%)				

SaO₂ — arterial oxygen saturation, SBP — systemic blood pressure, NA — not available.

*p < .001.

†p < .0001.

§p < .01.

use, the lack of investigations documenting their safety and efficacy, and their relatively high perioperative complication rate.

Many retrospective papers have been written in the literature on PDT since the preliminary proposal of Ciaglia et al⁹ in 1985, but only 4 randomized, pro-

TABLE 4. POSTOPERATIVE COMPLICATIONS

	<i>Hazard et al</i> ²		<i>Crofts et al</i> ³		<i>Friedman et al</i> ⁴		<i>Holdgaard et al</i> ⁵		<i>Totals</i>	
	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>
No. of procedures	24	24	25	28	26	27	30	30	105	109
Major bleed	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (>250 mL)	1 (>250 mL)	1 (3%)	1 (3%)	2 (2%)	2 (2%)
Minor bleed	1 (4%)	4 (17%)	3 (12%)	3 (11%)	1 (4%)	4 (15%)	2 (7%)*	9 (30%)	7 (7%)	20 (18%)
Stomal injection	1 (4%)†	8 (33%)	0 (0%)	1 (4%)	0 (0%)	4 (15%)	3 (10%)†	19 (63%)	4 (4%)	32 (29%)
Pneumothorax	1 (4%)	1 (4%)	0 (0%)	1 (4%)	0 (0%)	1 (4%)	0 (0%)	1 (3%)	1 (1%)	4 (4%)
Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (11%)	0 (0%)	0 (0%)	0 (0%)	3 (3%)
Subcutaneous emphysema	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Atelectasis	0 (0%)	0 (0%)	1 (4%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Aspiration	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	2 (7%)	1 (1%)	2 (2%)
Cuff leak	0 (0%)	0 (0%)	0 (0%)	2 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)
Total	3 (13%)	13 (54%)	4 (16%)	9 (32%)	2 (8%)	12 (44%)	6 (20%)	31 (103%)	14 (14%)	65 (60%)

*p < .05.

†p < .01.

TABLE 5. POST-DECANNULATION DEMOGRAPHICS

	<i>Hazard et al</i> ²		<i>Friedman et al</i> ⁴		<i>Total</i>	
	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>	<i>PDT</i>	<i>ST</i>
No. decannulated	11 (50%)	8 (33%)	5 (19%)	5 (19%)	16 (33%)	13 (25%)
Duration of tracheostomy	16.9 ± 12.9	22.0 ± 10.0	27.4 ± 22.1	30.1 ± 28.2	22	27
Days to tracheal closure			2.0 ± 1.7	8.4 ± 7.3		
Days to stomal closure			4.0 ± 2.0	12.2 ± 8.8		
Frequency of stenosis	2*	5				
Unspecified post-decannulation problems	3*	7				
Survival rate	54%	33%	58%	67%	56%	50%

Only 2 papers reported these data.

*p < .05.

spective studies have been identified.⁸⁻¹¹ When comparing these studies, we see a dramatic difference between the two techniques in the overall number of postoperative complications. The PDT group had a lower incidence of complications than the ST group (14% and 59%, respectively). These rates are comparable with those reported in nonrandomized, retrospective studies in the literature, ie, complication rates for PDT groups of 5.5% to 19%, and for ST groups of 6% to 63%.¹²⁻¹⁴

The most frequent complication in the ST group was stomal infections (29% incidence, versus 4% in the PDT group). The incidence in the PDT group is comparable with the 0% to 3% rate reported in the retrospective studies.¹²⁻¹⁴ Stomal infections in ST have been more widespread, with incidences ranging from 0% to 36%.¹⁵⁻¹⁷ The PDT method incorporates a smaller incision and more blunt dissection, which allow for less vascular and tissue disruption and may be an explanation for the decreased incidence of stomal infections.

The most frequent complication in the PDT group was bleeding (9%, versus 20% in the ST group). Minor bleeding was the second most common complication in the ST group. One patient in the PDT group required a transfusion after bleeding lasting for 15 hours, and 1 death occurred in the ST group after profuse bleeding from a presumed tracheoinnominate fistula.⁴ Rates of 2% to 10% for bleeding are reported in the PDT literature, and 1% to 40% in the ST literature.¹²⁻¹⁷ The ability to have a tracheostomy tube that fits snugly in the stoma allows for compression of bleeding vessels, the use of a smaller incision, and blunt dissection instead of cutting and transecting vessels and may explain the less frequent and less severe bleeding seen in the PDT group.

The rate of operative mortality was higher (but not statistically significant) in the ST group than in the

PDT group (3% versus 0%). These rates are again similar to what has been reported for the two techniques in nonrandomized, retrospective studies. Rates of 0% to 5% for the ST group^{12,16,17} and 0% to 3% for the PDT group¹² have been reported.

The long-term complication of tracheal stenosis was not examined in these randomized studies, but the incidence reported in the literature for PDT is between 0% and 10%, and that for ST is 0% to 16%.^{12,16-20} Tracheal stenosis is often asymptomatic until the tracheal lumen is reduced by more than 50% of its original diameter, and within 2 to 3 months after the removal of artificial airway devices.^{12,20} Stridor often does not occur until the tracheal diameter is 5 mm or less.²⁰ The most effective way to diagnose tracheal stenosis, both static and dynamic components, is with laryngoscopy.²⁰ Van Heurn et al²⁰ were able to show via histologic specimens that patients with PDT tubes for more than 10 days had destruction and necrosis of 1 or more tracheal rings, and those with subcricoid-placed tracheostomies had fractures of the cricoid cartilage. To decrease the risk of subglottic stenosis, it is recommended that PDT tubes be placed between the first and third tracheal rings.

Issues such as bronchoscopic guidance and costs for PDT were not covered in this paper, as we focused solely on the intraoperative and postoperative complications for two methods of tracheostomy. In conclusion, a fivefold difference between PDT and ST in the complication rate was noted. The complications that occurred were more severe and frequent in the ST group. From this meta-analysis of these 4 randomized studies, we conclude that PDT is a safer procedure for elective tracheostomy in patients with a normal-size neck. An ST or cricothyroidectomy should be done for patients with abnormal neck anatomy or for emergency access to the airway.

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PERIOPERATIVE AIRWAY COMPLICATIONS FOLLOWING PHARYNGEAL FLAP PALATOPLASTY

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This study was performed to determine the incidence and types of perioperative airway complications after pharyngeal flap palatoplasty. We conducted a retrospective chart review of 88 patients who underwent correction of velopharyngeal insufficiency between April 30, 1983, and April 30, 1997, in a tertiary care hospital. Some degree of airway obstruction developed in 7 patients. One child developed laryngobronchospasm and required immediate endotracheal intubation. He was successfully extubated without sequelae. Another patient developed severe obstructive sleep apnea and required flap revision. A third patient was found asystolic and apneic. She was immediately intubated; however, she subsequently died. Two patients aspirated blood, presumably resulting in pneumonia. They were managed with parenteral antibiotics. Another child developed worsening sleep apnea and required flap revision. One patient developed nasal obstruction that resolved with time. Airway compromise in patients who undergo pharyngeal flap palatoplasty can be a potentially fatal complication. Careful surveillance should be maintained over patients with underlying neurologic, craniofacial, or cardiopulmonary disorders.

KEY WORDS — airway, cleft palate, pharyngeal flap, velopharyngeal insufficiency.

INTRODUCTION

Pharyngeal flap palatoplasty is commonly used to treat hypernasality. This surgical procedure involves construction of a pharyngeal tissue flap designed to stop nasal airflow during speech.^{1,2} As a consequence of this procedure, both the nasal and oral airway are narrowed because of postoperative edema. In addition, the nasopharynx is obstructed by the flap, and the oropharynx is smaller because of flap construction.³ Superimposed on these anatomic changes, patients can have a depressed respiratory drive while recovering from general anesthesia.⁴ Many patients who undergo pharyngeal flap palatoplasty also have underlying craniofacial and neurologic conditions associated with smaller and structurally abnormal airways that can be easily collapsible as a result of hypotonia.⁴

Pharyngeal flap surgery inherently alters the airway and thus has the potential to cause a significant risk of perioperative airway complications. To determine the incidence and nature of these complications, we conducted a 14-year retrospective review of patients who underwent pharyngeal flap palatoplasty at our institution. All perioperative airway complications were recorded. Analysis of these data may help prevent further morbidity and death in this patient population.

MATERIALS AND METHODS

The medical records of all patients who underwent pharyngeal flap palatoplasty or revision pharyngeal flap palatoplasty from April 30, 1983, to April 30, 1997, were retrospectively reviewed. All available patients were included in this study. They all underwent a comprehensive evaluation by our craniofacial team. The evaluation included a perceptual speech evaluation assessing each patient's ability to produce oral speech sounds in single words and conversation. Hypernasality, nasal air emission, nasal substitution for oral consonants, omissions and substitutions of oral consonants, and compensatory articulation errors were noted. If the patient failed this screening, multiview videofluoroscopy was performed. The videofluoroscopic examinations were performed by a radiologist and an experienced speech-language pathologist. All views (lateral, Towne's, and submental vertex) were examined for evidence of velopharyngeal insufficiency. Palatal apposition, compensatory posterior pharyngeal wall movement, medial excursion of the lateral pharyngeal walls, and sphincter closure were all recorded. Patients with structurally based velopharyngeal insufficiency were referred for surgical evaluation.

The senior plastic surgeon (M.B.) performed all of the procedures with assistance from residents and

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TABLE 1. SURGICAL PROCEDURES SYNCHRONOUS WITH PHARYNGEAL FLAP PALATOPLASTIES

Procedure	Incidence	
	No.	%
Dental extraction	1	1.1
Dental restoration	1	1.1
Frenuloplasty	1	1.1
Tonsillectomy	1	1.1
Cleft lip revision	3	3.4
Oronasal fistula repair	4	4.5
Cleft nose revision	10	11.4
Myringotomy and tympanostomy tube insertion	15	17.0
Other	2	2.3

fellows. The patient demographic factors, underlying medical problems, cause of velopharyngeal insufficiency, anesthesia evaluation, and incidence and severity of perioperative airway complications were recorded for each subject. Patients who underwent concurrent surgical procedures were included. All patients were evaluated by the same experienced speech pathologist to assess the postoperative speech results.

A superiorly based pharyngeal flap was constructed in all cases except revision procedures. The flap design and dimensions were based on the speech pathologist's input and the results of videofluoroscopy. A vasoconstrictor with local anesthetic infiltrate was used in all cases, and the posterior pharyngeal donor site was uniformly closed. Nasal stents were not used. All patients had a tongue stitch placed to protect the airway on emergence from anesthesia and in the immediate recovery period. These tongue stitches were removed in the postanesthetic care unit. Steroids and nasopharyngeal airways were not routinely used. All patients were assigned to monitored beds. Pulse oximetry was added for patients with histories indicating a high risk of airway compromise.

RESULTS

There were 87 children and 1 adult in the study group. Of the 87 children, 48% were male and 51% were female. The mean age was 6 years (range, 11 months to 16 years). The adult was a 19-year-old woman. Eighty-seven patients (98.8%) underwent superiorly based pharyngeal flap procedures, and 1 patient underwent revision of a pharyngeal flap performed at another institution. Four of the 87 children underwent pharyngeal flap revisions for obstructive sleep apnea (2 patients) or flap dehiscence with residual velopharyngeal insufficiency (2 patients). Thirty-three patients (37.5%) underwent synchronous procedures (Table 1), some of which involved the airway (oronasal fistula repair, frenuloplasty, tonsillectomy).

Eighty-five patients (96.5%) were considered to

TABLE 2. CRANIOFACIAL SYNDROMES REPRESENTED IN PATIENTS UNDERGOING PHARYNGEAL FLAP PALATOPLASTIES

Syndrome	Incidence	
	No.	%
Floating-Harbor	1	1.1
Russell-Silver	1	1.1
Oral-facial-digital	1	1.1
Van der Woude's	1	1.1
Opitz	1	1.1
Popliteal pterygium	1	1.1
Facioauriculovertebral sequence	1	1.1
Fetal alcohol	1	1.1
Klippel-Feil	2	2.3
Pierre Robin	3	3.4
Velocardiofacial	4	4.5
Stickler	5	5.7

have a class I or II airway⁵ and were endotracheally intubated without difficulty. One patient with an anteriorly placed larynx required endotracheal intubation using a stylet to guide the tube in the larynx. Another patient with Stickler syndrome required 3 attempts for successful intubation. No fiberoptic intubations or tracheotomies were performed. One patient had a prior tracheotomy because of vocal cord paralysis.

Associated anatomic anomalies and medical conditions were seen in the majority of our patients. Twenty patients (23%) had cleft lip and palate. Twenty-two patients (25%) had a known craniofacial syndrome (Table 2). Neuromuscular deficits were seen in 5 patients, including the only adult in this study. Four patients had cardiac disease. One patient had thyroid disease, and 1 child had microcephaly.

Two patients required revision pharyngeal flap palatoplasty as a result of wound dehiscence and residual velopharyngeal insufficiency. One of these patients presented from an outside institution for revision surgery because of a poor speech outcome.

There were 7 patients with 14 perioperative airway complications (Table 3). Of these 7 patients, 3 required endotracheal intubation. One child developed laryngobronchospasm and required intubation. He was extubated within hours and suffered no sequelae. The second patient developed severe obstructive sleep apnea and nasal obstruction with significant oxygen desaturations and subsequently was intubated. This child has oral-facial-digital syndrome type I. She had some improvement of her airway and was extubated, but continued to have significant apnea and required revision pharyngeal flap palatoplasty. Although she improved after the operation, this patient continues on biphasic positive airway

TABLE 3. AIRWAY COMPLICATIONS OF PHARYNGEAL FLAP PALATOPLASTIES

Complication	Incidence	
	No.	%
Bleeding requiring transfusion	1	1.1
Laryngobronchospasm	1	1.1
Death	1	1.1
Airway obstruction	2	2.3
Nasal obstruction	3	3.4
Aspiration	3	3.4
Pneumonia	3	3.4

pressure for moderate obstructive sleep apnea. The third patient was found asystolic, apneic, and cyanotic on the third postoperative day. She was immediately intubated. Vomitus was noted in her airway. She died shortly afterward. The autopsy findings were remarkable for bilateral lower lobe pneumonias and blood in the stomach.

Two patients aspirated blood, presumably resulting in pneumonia. One had significant bleeding on the fourth postoperative day and required transfusion. She developed a left lingular pneumonia and was managed successfully with parenteral antibiotics. The other patient was suspected to have aspirated blood shortly after surgery. She had significant desaturations on the evening of surgery. She was managed in the intensive care unit with parenteral antibiotics and supportive measures. She improved significantly and was discharged home on the fifth postoperative day.

One patient developed nasal obstruction and worsening sleep apnea. (The degree of preoperative apnea was unclear.) This child required flap revision and has subsequently done well. One other patient developed nasal obstruction that resolved with time.

DISCUSSION

The results of this study demonstrate a 16% incidence of perioperative airway complications in 7 patients (7.9%) after superiorly based pharyngeal flap palatoplasty and revision. Five of these patients had more than 1 airway complication. All airway complications occurred by the fourth postoperative day. The majority of our patients had anatomic airway anomalies or preexisting medical conditions. However, no one anomaly or medical condition was more likely to be related to airway compromise.

Only 2 patients required revision pharyngeal flap palatoplasty as a result of residual velopharyngeal insufficiency. One of these patients presented initially for revision surgery because of a poor speech outcome.

Several studies have examined the postoperative complications of pharyngeal flap surgery. Nylén and

Wählin⁶ reported hemorrhage to be the major complication, as well as the primary reason for airway compromise in these patients. Owsley and Blackfield⁷ also reported bleeding as the major complication. One of 3 patients with respiratory embarrassment in that series actually had a blood clot in his larynx. Valnicek et al⁸ reviewed the perioperative complications of superiorly based pharyngeal flaps and noted that bleeding and airway obstruction were the most common complications. Approximately one third of patients with bleeding had airway compromise. In our study, the incidence of bleeding was significantly lower than that in earlier reviews. However, when hemorrhage was present, it was associated with airway compromise, primarily aspiration pneumonia.

Another factor that influences airway obstruction in these patients is the number of other airway procedures performed at the time of pharyngeal flap palatoplasty. Both Wray et al⁹ and Graham et al¹⁰ have reported a significantly increased risk for airway obstruction in patients who undergo concomitant palatoplasty and pharyngeal flap surgery. Argamaso et al¹¹ discourage synchronous tonsillectomy and pharyngeal flap procedures, because bleeding complications could be increased and because the potential for adherent scars to form in the areas of the tonsillar pillars, palate, and pharyngeal wall and cause airway obstruction is increased. No patients in this study underwent combined palatoplasty with pharyngeal flap surgery. Only 1 patient underwent tonsillectomy and pharyngeal flap surgery concomitantly. None of the patients who underwent pharyngeal flap surgery synchronous with oronasal fistula closure, frenuloplasty, or tonsillectomy had airway embarrassment, although 1 patient had a wound dehiscence and recurrence of her fistula. Perhaps one of the reasons that the incidence of perioperative airway obstruction is relatively low in our study is the tendency to *not* schedule combined airway procedures. Less dissection results in less edema and, subsequently, less airway obstruction.

Obstructive sleep apnea is a well-known complication of pharyngeal flap surgery.^{12,13} Orr et al¹⁴ demonstrated a 90% incidence in the immediate postoperative period in these patients. Obstructive sleep apnea is even more common in patients with craniofacial anomalies.¹⁵ Kravath et al¹⁶ reported airway obstruction in 3 children; 2 of these patients had velocardiofacial syndrome. Jackson et al¹⁷ described 3 cases of airway compromise in pediatric patients with Pierre Robin syndrome. In addition, patients with underlying neurologic deficits have an increased incidence of obstructive sleep apnea. Cadieux et al¹⁸ and Salomonson et al¹⁹ presented cases of obstructive

sleep apnea following pharyngeal flap surgery in patients with myotonic dystrophy.

Interestingly, the incidence of obstructive sleep apnea in our review is lower than that reported in previous studies.¹²⁻¹⁴ Even more surprising is the fact that more than one quarter of our study population had craniofacial anomalies (most of which were associated with obstructive sleep apnea) and neurologic deficits, yet only 2 patients had evidence of postoperative obstructive sleep apnea. One explanation for the decreased incidence of airway obstruction observed in our study is our rigorous multidisciplinary preoperative evaluation of all patients. Multiple histories and examinations are completed by geneticists, speech-language pathologists, plastic surgeons, and otolaryngologists and are thoroughly discussed. In some cases, preoperative sleep studies are obtained to further evaluate high-risk patients. Tonsillectomy, if indicated, is usually performed at least 6 weeks before pharyngeal flap surgery. Any underlying medical condition is addressed and corrected before surgery. Because high-risk patients are identified before surgery, they can be monitored more closely for postoperative complications. Further, because factors that may contribute to postoperative airway complications are identified and addressed before surgery, the width

of the pharyngeal flap does not have to be altered to compensate for these factors. This approach supports the excellent speech results obtained in this study.

Another factor that may help account for the low incidence of airway obstruction is the fact that the senior surgeon (M.B.) performed all pharyngeal flap procedures. Because of his extensive experience, he is able to design flaps of appropriate width in a shorter time, so the patients have less postoperative edema and airway obstruction.

CONCLUSION

Although uncommon, airway compromise following pharyngeal flap palatoplasty can be a potentially fatal complication. Seven patients (7.9%) had airway compromise; 5 of these patients had more than 1 airway complication in the postoperative period, and 1 child died. All of the airway complications occurred within the first 4 postoperative days. Thorough histories and physical examinations performed by a experienced craniofacial team are paramount in identifying high-risk patients. Even so, each patient should be monitored closely after surgery. Careful surveillance should be maintained over patients with an underlying neurologic impairment, craniofacial disorder, or cardiopulmonary insufficiency.

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TRACHEOBRONCHIAL EXTENSION OF RECURRENT RESPIRATORY PAPILLOMATOSIS

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Endobronchial and pulmonary dissemination reportedly occurs in 5% of patients with laryngeal papillomatosis. It is more frequently observed in the juvenile form, and carries significant implications for treatment. In this study, we review our experiences with pulmonary and endobronchial extension of laryngeal papillomatosis. The records of the 52 patients with laryngeal papillomas treated at our institution since 1980 were reviewed. Twenty-nine percent of the patients (N = 15) developed tracheobronchial extension; 7% (N = 4) demonstrated pulmonary involvement. The birth history, race, sex, age at onset of symptoms, presenting symptoms, site and type of papillomas, surgical procedures, other methods of treatment, complications, and mortality data were analyzed. Eighty percent of the patients with tracheobronchial involvement were born to mothers with a positive history of vaginal condylomas. Pulmonary changes in 4 patients were observed on either chest radiographs or computed tomography and were manifested as multiple parenchymal nodules in 3 of the 4 patients. Pneumatoceles, cavitory empyema, and multiple recurrent pneumonias were the predominant complications of pulmonary involvement. Of the 15 patients with tracheobronchial extension, 80% (N = 12) required tracheotomy before their presentation to us. The number of multiple surgical procedures performed to remove papillomas ranged from 7 procedures in 1 patient with a solitary tracheobronchial lesion to more than 100 procedures in 2 patients with diffuse bronchopulmonary papillomatosis. As our study shows, tracheobronchial involvement continues to complicate surgical treatment in this challenging disease process.

KEY WORDS — laryngeal papilloma, pneumatocele, tracheobronchial extension.

INTRODUCTION

First described in the 17th century as "warts in the throat," laryngeal papillomas have come to be recognized as the most common benign neoplasm of the larynx in children.¹ The incidence is reported to be approximately 4.3 per 100,000 children per year. Pulmonary and distal tracheal spread of papillomatosis reportedly occurs in 5% of patients.² The clinical course of recurrent respiratory papillomatosis (RRP) is quite variable and unpredictable. It is potentially a life-threatening condition with a high rate of morbidity and high economic cost. A particularly adverse influence is exerted by progression of the disease to involve the tracheobronchial tree. Although extension to the tracheobronchial tree is infrequently encountered in patients who have not required previous tracheotomy, some patients experience relentless progression and tracheotomy becomes necessary. According to Kashima et al,³ 15% of patients with the juvenile form of RRP require tracheotomy for airway complications and management. Tracheobronchial extension is linked to a previous tracheotomy in more than 95% of reported cases.⁴

The factors that determine spontaneous regression versus persistent or progressive disease are still unknown. Recent theories to explain the discrepancies in outcome include differences in infecting viral DNA

and host or immune factors.⁵ The most recent literature links respiratory papillomas to human papillomavirus (HPV) subtypes 6 and 11 in more than 95% of papillomas isolated from the pediatric larynx. Typing of papillomas extending into the trachea has shown similar results.⁶ Quiney et al⁷ found the form of disease characterized by bronchial extension to be more commonly linked to subtype 11. However, Rimell et al⁸ found in their initial study that the infecting HPV subtype had little influence on the clinical outcome in patients with laryngeal papillomatosis. Both subtypes 6 and 11 were associated with nuclear atypia, carcinoma in situ, and squamous cell carcinoma in laryngeal papilloma patients, but subtype did not affect disease progression.⁸ However, Rimell et al⁹ later, using polymerase chain reaction, found that HPV subtype 11 significantly affected the clinical outcome, resulting in a more aggressive disease course. This was originally suggested by Mounts and Kashima,¹⁰ who found HPV subtype 6C (which has since been found to be subtype 11) to be associated with a more obstructive course. The literature dealing with bronchial extension and pulmonary complications is scant, owing primarily to its infrequent occurrence.

The present report is a study of 52 patients treated for RRP at the University of Mississippi Medical

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Center over the past 18 years. Most important, 15 of these patients had tracheobronchial extension. In this group of 15 patients, 11 had disease extending into the tracheobronchial tree, and 4 had extension into the pulmonary parenchyma. The goal of this investigation is to review these cases of RRP with specific attention to tracheobronchial extension, as there have been few such studies of distal papillomatous disease.

METHODS

The medical records of the 52 patients who were treated for RRP at our medical center over the past 18 years were reviewed. Clinical data were abstracted from the records and statistically analyzed. The records were examined for 1) patients' sex and race, 2) symptoms leading to the diagnosis, 3) age at onset of symptoms, 4) history of tracheotomy, 5) specific sites of tracheal and bronchial involvement, 6) numbers and methods of surgical procedures, 7) pulmonary complications, and 8) course of the disease.

RESULTS

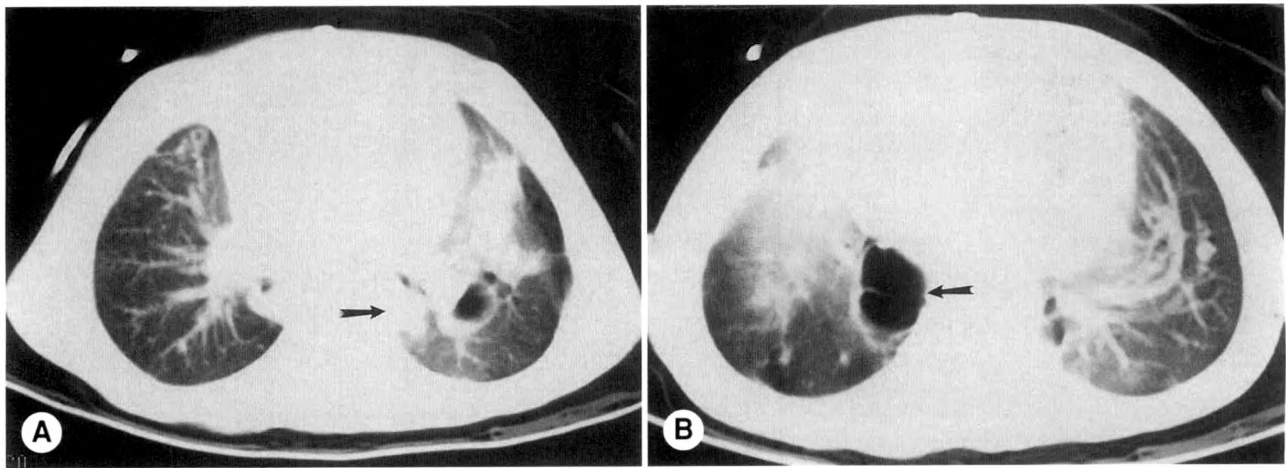
Sex and Race. Of the 52 patients with a diagnosis of RRP, 21 were female and 31 were male. Eleven patients had papillomatosis extending into the tracheobronchial tree, and 4 had additional extension into the pulmonary parenchyma. Of the total, 36 were African American (69%) and 16 were white (31%). These numbers do not reflect exactly our overall patient population, which is 55% African American and 45% white. In the 15 patients who had tracheobronchial or pulmonary extension, there were no statistically significant differences in sex or race as compared to the patients with laryngeal involvement alone. However, there were trends that were noticed in the entire group. A higher incidence of regression occurred in African American male patients, and female patients (regardless of race) were more likely to have persistent or progressive disease. All 4 patients with pulmonary involvement were female. Forty of the patients had complete records detailing the presence or absence of maternal vaginal condylomas. All 15 patients with tracheobronchial or pulmonary involvement had available maternal records. Eighty percent ($N = 12$) of these patients were born to mothers with a positive clinical history of vaginal condylomas. Of the remaining 37 patients, maternal records were available for 25, and only 48% ($N = 12$) of these patients were born to mothers with a clinical history of vaginal condylomas.

Symptoms. In the 15 patients who had tracheobronchial extension, the most common symptom signaling tracheobronchial progression was airway obstruction or stridor. Increasing stridor was noted in 12 of

the 15 patients as they progressed from glottic to tracheobronchial involvement. The initial symptom of all of these patients when they presented with glottic involvement was hoarseness. This was the same initial symptom as that in the patients with disease that remained limited to the glottis. Hoarseness was the initial complaint in 34 of these 37 patients (91%). Increasing airway obstruction was a distant second in initial presenting symptoms, with 12 of the 37 patients (32%) requiring attention owing to airway compromise.

Age at Onset of Symptoms. The age at onset of symptoms was usually obtained from the patient's mother or a referring physician, as most of the patients were initially seen by a referring physician. Of the 37 patients with disease limited to the larynx, the majority of patients presented between the ages of 7 months and 1 year; three fourths of the patients manifested symptoms by the age of 3 years. In the tracheobronchial extension group, there was no significant difference in age of initial presentation. Approximately 2 years elapsed between the time of initial diagnosis and the time that tracheal or tracheobronchial extension was seen in 6 of the 15 cases. Twelve of the 15 patients had tracheal involvement by the age of 8 years. The remaining 3 patients progressed to tracheal involvement at ages 9, 11, and 12 years. The earliest age at which tracheal extension was seen was 3 years ($N = 2$).

History of Tracheotomy. In our experience, 13 of the 52 patients managed required tracheotomy for airway management. The great majority of the patients (11 of the 13) had a tracheotomy placed by the referring physician before presentation to our center. The reason given for tracheotomy by referring physicians was either stabilization of the airway or glottic stenosis secondary to repeated laser ablations in all of the referred cases. In the 2 patients who required tracheotomy at our institution, the tracheotomy was placed for excessive glottic scarring and stenosis secondary to previous multiple laser ablations of their glottic disease. All of the patients requiring tracheotomies tended to have more aggressive disease even before tracheotomy, as they required an average of 6 procedures per year before tracheotomy. The average number of procedures per year in patients with glottic involvement only was 3. Of these 13 patients, 11 subsequently developed tracheal or tracheobronchial extension. One patient was found to have tracheal extension at the time of tracheotomy. The patient who had tracheotomy without progression to tracheobronchial extension was decannulated at age 13, when her papillomatous disease regressed with the onset of puberty. The average age at tracheotomy was 4 years, with the youngest pa-



Axial computed tomograms of chest. A) Pneumatocele (arrow) in pediatric patient with tracheobronchial papillomas. There is also evidence of pulmonary fibrosis. B) Pediatric patient with bronchial extension of laryngeal papillomas who developed right perihilar pneumatocele (arrow).

tient requiring tracheotomy at 2 years and the oldest patient at 16 years. The average time interval between onset of tracheotomy placement and tracheal papillomatous involvement was 17 months. When possible, every attempt was made to decannulate the patients in an expedient manner. Three of the patients were successfully decannulated after regression of their papillomas. Only 1 of these patients now requires intermittent laser ablation.

Sites of Tracheobronchial Involvement. The most common site of involvement in the 52 patients was the true vocal cord ($N = 48$), followed by concurrent supraglottic involvement in 20. Fifteen of the patients had tracheal, bronchial, or pulmonary extension from their initial glottic lesions (11 in the tracheobronchial tree, and 4 in the pulmonary parenchyma). The most common sites of tracheal involvement were the mucocutaneous junction at the tracheotomy site and the mid-trachea, corresponding to the distal end of the tracheotomy tube. Eleven of the patients had papillomas involving these two regions. In the other 4 patients, papillomas extended down to the carina bilaterally, with the majority of the papillomas on the posterior tracheal wall. Each of these 4 patients had bronchial extension, with the right proximal bronchus more severely affected than the left. These 4 patients also had evidence of pulmonary parenchymal disease on computed tomography (CT) of the chest.

Numbers and Methods of Surgical Procedures. The average number of surgical procedures was dependent upon the duration and extent of disease, with the more aggressive cases requiring multiple procedures. The number of surgical procedures ranged from 1 to 168. One patient who had a prolonged course required more than 160 procedures over the course of 7 years, and another patient required more than 120 procedures over 6 years. A single procedure was per-

formed in a 3-year-old child who had complete resolution after a single CO₂ laser ablation. An average number of 6 procedures over the course of the disease was performed in patients with disease limited to the glottis. This was found to be an average of 3 procedures per year in the laryngeal involvement group. In the patients with tracheobronchial extension, an average of 32 procedures over the course of the disease was required. This represents an average of 12 procedures per year.

Pulmonary Complications. Multiple complications were found in the patients with tracheobronchial dissemination, including pneumonia in 4 patients, tracheal stenosis in 3, lung abscess in 2, pneumatocele in 2, and empyema in 1. The most significant pulmonary complication was the occurrence of pulmonary pneumatoceles in 2 of the 4 patients who had bronchial involvement. These were diagnosed by CT scans of the chest. Both patients had prolonged courses of RRP requiring more than 100 surgical procedures in each patient. The first patient presented with a productive cough, and pneumonia was suspected. When a chest x-ray study was inconclusive, a CT scan of the chest revealed a right lower lobe peripheral pneumatocele. The pediatric pulmonary service initially treated the patient with a 7-day course of antibiotics and then conservatively managed the lesion with serial CT scans (see Figure, A). The patient clinically demonstrated improvement, but the pneumatocele failed to resolve. The second patient presented with much the same symptoms and was worked up in the same manner. A chest CT scan revealed a large perihilar right lower lobe pneumatocele, which was also managed conservatively (see Figure, B).

Recurrent pneumonias were seen in the group of patients with tracheobronchial and pulmonary disease, and 2 of these patients developed subsequent

TABLE 1. COMPARISON OF REMISSION RATES IN DISEASE LIMITED TO GLOTTIS IN DIFFERENT GENDER AND RACIAL GROUPS

Gender and Racial Group	No. of Patients With Glottic Involvement	Patients With Disease Remission	
		No.	%
White female	4	3	75
African American female	8	7	87
White male	7	7	100
African American male	18	18	100

lung abscesses. The patients were initially treated with antibiotics for their pneumonia, but concern of lung abscess was heightened when the patients continued to have persistent coughing and production of foul-smelling sputum. Chest CT scans revealed thick-walled lung abscesses, with both abscesses being associated with anaerobic bacteria according to sputum cultures. The patients were placed on intravenous clindamycin phosphate and had resolution of the abscesses within 6 weeks, as shown by follow-up chest CT scans. One patient developed a second lung abscess approximately 8 months after the first abscess was treated. This second abscess progressed to an empyema despite intravenous antibiotics. Surgical intervention was required, with tube thoracostomy placement for drainage and resolution of the empyema.

Three patients developed tracheal stenosis of 25% to 50%. In all 3 patients, the stenosis was encountered at the site of the distal end of the tracheotomy tube.

Disease Course. Of the 37 patients with isolated laryngeal involvement, 35 have had regression of their disease. All regressions occurred at about the puberty onset. There were no significant differences found between the patients who had regression at puberty and the 2 patients who continued to have disease involvement after puberty. There were no differences in the average number of procedures per year, the age at onset, or the location of the papillomas, as all were either glottic or supraglottic. Typing of HPV was not performed, and questions pertaining to reflux were not recorded. The 2 patients with continued disease have biyearly follow-up and have not required ablation in 3 years.

The 15 patients with tracheobronchial involvement have been found to harbor a much more persistent disease, with only half having disease remission. Again, this half had disease remission at the age of puberty onset. An effort was made to determine significant characteristics of the patients who had disease regression versus patients with disease progres-

TABLE 2. COMPARISON OF REMISSION RATES IN TRACHEOBRONCHIAL DISEASE IN DIFFERENT GENDER AND RACIAL GROUPS

Gender and Racial Group	No. of Patients With Tracheobronchial Involvement	Patients With Disease Remission	
		No.	%
White female	2	0	0
African American female	7	2	28
White male	3	2	66
African American male	3	3	100

sion in the patients with tracheobronchial involvement. There were no statistical differences between the patients with disease regression versus continuation with regard to number of procedures per year or age at onset. Both groups of patients had disease involving the tracheobronchial tree; however, no patient with pulmonary involvement had regression. A higher incidence of regression occurred in black male patients; however, this was not a statistically significant difference. Female patients were more likely to have progression of disease. Again, this was not a statistically significant difference (Tables 1 and 2). The average age at which regression of disease was first noted as determined by intraoperative findings was 7 years of age, and remission was usually complete by 12 years of age. When we compared the patients with tracheobronchial involvement to the patients with disease limited to the glottis, we found that the patients with tracheobronchial involvement had an earlier onset of disease. These patients presented with disease onset an average of 2 months earlier than the patients with disease limited to the glottis. The patients with tracheobronchial involvement required an average of 12 procedures per year, whereas the patients with isolated glottic involvement required an average of 3 procedures per year. In the 4 patients who progressed to pulmonary involvement, all were female and had disease onset an average of 2.5 months earlier than the patients who had disease confined to the glottis. These 4 patients all had tracheotomy by the age of 2 years secondary to glottic scarring from multiple surgical procedures or for stabilization of the airway.

Unfortunately, HPV typing was not done on pathology specimens; it would have allowed us to determine any differences in subtypes between the patients with regression and those with progression. All pathological reports indicated squamous papillomatous growths, and no atypia was noted. Lindeberg and Elbrond¹¹ reported on 3 patients who had squamous cell carcinoma that developed from RRP. Each patient had previously been treated with radiotherapy.¹¹ In our series, no progression of disease to squamous

cell carcinoma has been noted. However, none of our patients have received radiotherapy as adjuvant treatment for their disease. Of the 4 patients with bronchopulmonary involvement, 1 died of asphyxia, and the other 3 continue to have serial laser ablation at the ages of 4, 6, and 12 years.

DISCUSSION

Recurrent respiratory papilloma has been extensively studied, so that advances have been made in its diagnosis, treatment, and prevention. However, there have been few studies that have concentrated on its tendencies in the presence of tracheobronchial and pulmonary extension. We have attempted to present our experience with 15 patients who were followed as their laryngeal papillomas progressed to tracheobronchial or pulmonary involvement.

Pulmonary and distal tracheal spread of papillomas reportedly occurs in 5% of patients with RRP.² However, a higher incidence of tracheobronchial involvement was found in our series of patients. Of the 52 patients treated for RRP at our institution, 11 patients (21%) developed tracheobronchial extension, and 4 patients (7%) progressed to pulmonary involvement. The increased incidence of tracheobronchial involvement may be explained by an increased need for tracheotomy in the management of airway compromise. The majority of the patients had tracheotomy performed at outside hospitals before referral to our medical center. Weiss and Kashima¹² have reported a higher incidence of tracheobronchial extension of papillomas after tracheotomy. Twelve of our 15 patients did have tracheotomy before development of tracheobronchial extension. A 13th patient received a tracheotomy after onset of tracheal extension. The average time interval between the tracheotomy and the onset of tracheal extension was 17 months. Tracheotomy significantly affected the disease process; those with tracheobronchial extension had a longer course of disease, many more surgical procedures, and also more complications related to their disease process. Shapiro et al¹³ reported on their experience with 43 RRP patients, 11 of whom required tracheotomy, and concluded that patients requiring tracheotomy may harbor a more aggressive form of the disease from the onset, as their tracheotomy patients presented at earlier ages, required more surgical procedures, and had more obstructive disease. Our tracheotomy patients differed from their series in that they were more likely to develop distal disease (73%, compared to 54% in their series). Our patients who required tracheotomy, as consistent with the aforementioned group, presented at earlier ages than the nontracheotomy group and also required more procedures before tracheotomy than the non-

tracheotomy group. Our study supports the assertion of Shapiro et al that tracheotomy patients may have more aggressive disease from the onset. It also confirms the significant correlation between tracheotomy and distal tracheobronchial spread.

When the patients were compared according to race and sex, we found a tendency (though not statistically significant) for black male patients to have a favorable prognosis, with earlier regression, as well as a higher incidence of regression, of their disease. The female patients, regardless of their race, were noticed to have more progressive disease. This is evidenced by the fact that all 4 of the patients with pulmonary extension were female.

The clinical triad of a firstborn delivered vaginally to a very young teenage mother has been linked to juvenile-onset RRP.¹⁴ In the 4 patients who developed pulmonary parenchymal involvement, 3 patients had the complete triad, and the fourth patient had 2 of the 3 components of the triad. The patient's mother was in her early twenties at the time of delivery. In the 11 patients with tracheobronchial involvement, 8 patients (72%) were born to mothers with a history of vaginal condylomas.

With an increased incidence of tracheobronchial and pulmonary extension, we also found multiple complications that were linked to the papillomatous disease course. One significant complication is the occurrence of pneumatocele in the presence of pulmonary invasion by RRP. Pneumatocelles appear as cystic foci in the lung and are usually acquired lesions resulting from necrosis of bronchopulmonary tissue during infection, with an air-filled cystic space resulting from a formerly patent airway. High expiratory pressures secondary to proximal obstruction have commonly been implicated as the cause of pneumatocelles. They are often linked to previous bacterial pneumonia, aspiration pneumonia, emphysema, and lymphangiectasis.¹⁵ The most common complication of pneumatocele is abscess with resultant fibrosis. The majority of these abscesses require intravenous antibiotics and surgical drainage, as did our 2 patients. Both pneumatocelles occurred in the right lower lobe, probably because of direct extension, as the right bronchus is more prone to aspiration than the left bronchus. Kramer et al¹⁶ first reported experience with pulmonary manifestations in 7 patients with respiratory papillomas. They described the characteristic manifestation of papillomatosis as a round pulmonary nodule, which was also seen frequently in our 4 patients. They also found central cavities of necrosis, but did not find pneumatocelles as described in 2 of our 4 patients. The other significant difference in our findings is the distribution of the pulmo-

nary lesions. Two of our 4 patients manifested lesions proximal to the respiratory bronchioles. All of the patients of Kramer et al had pulmonary disease distal to the respiratory bronchioles. Distal seeding has been the proposed cause of pulmonary dissemination. The scarcity of lesions proximal to the respiratory bronchioles was thought to be due to the ability of the cough reflex, as well as mucociliary clearance, to rid the lungs of proximal seedings.¹⁶ However, in our patients, we did find lesions that were more proximal than previously reported.

A second complication, occurring with almost equal frequency as the pneumatocele but resulting in a more prolonged hospital course, was the lung abscess. Classically, anaerobes have been identified as the most common cause of lung abscess. Abscess is typically located in the basal segments of the lower lobes, and microbiological diagnosis is generally not required. Bartlett and Gorbach¹⁷ recommend treatment with intravenous antibiotics until the patient is afebrile and shows clinical improvement (4 to 8 days). Oral antibiotics are then given for a total of 6 to 8 weeks. Despite aggressive antimicrobial therapy, they found that 10% of lung abscesses required surgical intervention,¹⁷ as did 1 of our cases. Two of our patients developed 3 lung abscesses; 2 of the abscesses were managed conservatively, and the third required thoracotomy tube insertion after progression to empyema. A mixture of anaerobic bacteria and papillomas was found in the drained empyema fluid.

Tracheal stenosis is a third complication that occurred in our patient population with tracheobronchial extension. Acquired stenosis, as in our cases, is accompanied by extensive scarring, perichondritis, and loss of cartilaginous support, which may complicate surgical resection of papillomas. The degree of tracheal stenosis was assessed by rigid bronchoscopy at the time of laser vaporization of the papillomas. All 3 patients had stenosis limited to the site of the distal end of the tracheotomy tube, with no pa-

tient having greater than 50% narrowing of the airway. The patients had previously had an average of 26 laser ablations of their tracheal papillomas before tracheal stenosis became evident. The cases of stenosis have not required open surgical reconstruction.

Our patients with pulmonary involvement were followed with routine chest x-rays, pulmonary function tests, and CT. High-resolution chest CT has proven diagnostic of pulmonary blebs and pneumatoceles in more than 97% of the reported cases.¹⁸ This modality proved to be the gold standard in diagnosing pulmonary extension of RRP. Radiographs were used to follow the progression of pulmonary disease.

Various adjuvant therapies for RRP, including radiotherapy, photodynamic therapy, acyclovir, and interferon, have been used. Leventhal et al¹⁹ recommend initiating interferon therapy in patients who require surgical therapy more than 4 times yearly for RRP. In our series, interferon was used as an adjuvant therapy in 3 of the 15 patients prior to their tracheobronchial extension. Two of the patients did not tolerate treatment because of adverse side effects, and the third patient exhibited no improvement despite 8 months of therapy. This same patient also was treated with photodynamic therapy, but had no response.

Although surgery is only palliative in patients with tracheobronchial extension of RRP, it remains the treatment of choice.² The surgical goals include maintenance of an airway, resection of papillomatous tissue, and avoidance of mucosal injury so as to limit permanent damage and scarring. When extension of lesions into the trachea and bronchus becomes obstructive, flexible endoscopic laser delivery systems are helpful in achieving these goals. However, tracheobronchial complications, as in our study, continue to complicate surgical treatment of this challenging disease process.

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INTERNATIONAL CONFERENCE ON NEWBORN HEARING SCREENING DIAGNOSIS AND INTERVENTION

The International Conference on Newborn Hearing Screening Diagnosis and Intervention will be held in Milan, Italy, October 12-14, 2000. In Europe, contact Dr Ferdinando Grandori, Center of Biomedical Engineering, Polytechnic of Milan, piazza Leonardo da Vinci 32, I-20133 Milan, Italy; fax +39.02.2399.3360; e-mail NHS2000@biomed.polimi.it. In the United States, contact Dr Deborah Hayes, The Children's Hospital, 1056 E 19th Ave, B030, Denver, CO 80218; telephone (303) 861-6424; fax (303) 764-8220; e-mail: Hayes.deborah@tchden.org.

OUTCOMES ASSESSMENT FOLLOWING TREATMENT OF SPASMODIC DYSPHONIA WITH BOTULINUM TOXIN

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Spasmodic dysphonia (SD), a disabling focal dystonia involving the laryngeal musculature, is most commonly treated by the intramuscular injection of botulinum toxin (BTX). Although the treatment is well tolerated and generally produces clinical voice improvement, it has never been statistically shown to alter the patient's perception of voice quality or general health. Declining resources for medical care mandate that treatment outcomes be documented. A prospective analysis of the effects of BTX on the patient's perception of voice and general health was undertaken. The Voice Handicap Index (VHI) and Short Form 36 (SF-36) surveys were administered to patients before treatment and 1 month after. Pretreatment and posttreatment scores were analyzed with a Student's *t*-test. On the VHI, improvements in the patients' perception of their functional, physical, and emotional voice handicap reached statistical significance ($p \leq .0005$). On the SF-36, patients had statistically significant improvements in mental health ($p \leq .03$) and social functioning ($p \leq .04$). Treatment of SD with BTX significantly lessened the patients' perception of dysphonia. In addition, it improved their social functioning and their perception of their mental health. These outcome measures justify the continued treatment of SD with BTX.

KEY WORDS — abductor, adductor, botulinum toxin, dystonia, spasmodic dysphonia, Voice Handicap Index.

INTRODUCTION

Spasmodic dysphonia (SD), a focal dystonia involving the laryngeal musculature and brain stem, affects a small percentage of the population of the United States.¹ The affected patients are usually otherwise healthy, but are often disabled by the dysphonia, which increases the effort required to speak and decreases the intelligibility of their verbal communication.

Spasmodic dysphonia is part of the broad neurologic disease group of movement disorders and is subclassified as a focal dystonia.² Focal dystonias are characterized by inappropriate and excessive efferent activity in motor neurons in limited areas. During task-specific muscle stimulation, centrally induced increases in muscle contraction (spasms) occur.³ These spasms interrupt the normal muscular contraction pattern and decrease the overall efficiency of movement. The result is that the spasms increase the effort required to perform a task and often lead to the perception of discomfort.

Current treatment for SD is aimed at weakening the degree of muscle spasms by altering the neural input to the affected muscles.⁴ This strategy is partic-

ularly effective in adductor SD, in which spasms of the thyroarytenoid (TA) and lateral cricoarytenoid (LCA) muscles result in excessive laryngeal closure. However, when spasms of the posterior cricoarytenoid muscles result in excessive laryngeal opening, as in abductor SD, weakening the muscles that open the larynx can result in respiratory compromise before achieving a significant reduction in the degree of spasms.

Weakening of laryngeal closure in adductor SD can be achieved either permanently, by surgically interrupting the neural supply to one vocal fold, or temporarily, by chemically denervating portions of the adductor muscles. Surgical creation of permanent unilateral paralysis resulting in glottal incompetence can produce significant relief of spasms, but may result in a breathy dysphonia.⁵ In addition, if the muscle undergoes spontaneous reinnervation, return of tone to the LCA-TA complex often results in a medial position of the immobile vocal fold that is accompanied by the return of spasms.⁶ Therefore, the surgical results of unilateral denervation are unpredictable. Chemical denervation, although temporary in effect, allows better control of the degree of laryngeal weakening and has become the preferred method

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of treatment.²

Chemical denervation is most commonly achieved with botulinum toxin type A (BTX),⁷ which binds noncompetitively with the presynaptic neural end plate to prevent the release of acetylcholine.³ It was studied prospectively as an agent for the treatment of blepharospasm. It was shown to be a relatively safe and reliable drug for use and therefore gained approval by the US Food and Drug Administration (FDA) for use in treatment of blepharospasm, strabismus, and hemifacial spasm.⁸ Subsequently, BTX was also shown to reliably weaken the laryngeal adductor muscles for the relief of adductor SD,³ yet BTX has not received approval of the FDA for this use. Therefore, despite the body of literature that supports the use of BTX for the symptomatic relief of SD, many insurance companies today still consider its use experimental and refuse to cover the costs of injection for their subscribers.

This study was undertaken to determine whether the treatment of SD with BTX made a statistically significant impact on patients' perception of their dysphonia and to determine whether treatment of SD affected their perceived quality of life.

METHODS

A prospective, nonrandomized study was performed on consecutive patients who underwent their first treatment for adductor SD at the Vanderbilt Voice Center between June 1998 and December 1998. Patients were excluded if they had undergone prior treatment with BTX at an outside institution. Thirty-eight patients (30 women and 8 men) were administered the standard US version of the Short Form 36-Item Health Survey⁹ (SF-36; Medical Outcomes Trust, Boston, Mass) and the Voice Handicap Index (VHI), a questionnaire designed to measure the functional, physical, and emotional effects produced by dysphonia.¹⁰

In accordance with Vanderbilt University Internal Review Board policy, informed consent was obtained from the subjects. The patients completed the pretreatment questionnaires and were treated with BTX, which was administered percutaneously with electromyographic guidance. Each patient received 2.5 mouse units of BTX in 0.1 mL of normal saline solution in each TA muscle. A 27-gauge Teflon-coated needle was inserted into the TA muscle. The patients were asked to sustain an /i/ vowel to verify placement. When adequate placement was obtained, the BTX was injected. The opposite TA muscle was injected in a similar manner.

One month after treatment, the patients were asked

to complete the second set of questionnaires. To improve compliance, the patients were given an addressed, stamped envelope in which to return the questionnaires. If the questionnaires were not received within 1 week of the deadline, the patients were telephoned and asked to complete the questionnaires.

The questionnaires were collected and scored according to the established guidelines.^{9,10} The software program Statview SE + GraphicsTM was used to perform paired 2-tailed Student's *t*-tests on the pretreatment and posttreatment responses for each of the categories from the questionnaires. Unpaired *t*-tests of pretreatment and posttreatment SF-36 data were made against known data from US normals.⁹

RESULTS

Thirty-eight patients completed the pretreatment and posttreatment questionnaires (8 men and 30 women). The average age of onset of SD was 45 years (range, 21 to 71 years), with patients having waited an average of 7.5 years between the onset of SD and receiving their first injection (range, 6 months to 30 years). The voice symptoms developed over an average of 2 years. Four patients developed dysphonia suddenly, whereas 2 patients stated that their symptoms took more than 10 years to develop. The SD began after an illness or physical trauma in 15 patients, after emotional trauma in 7, and without any associated events in 16.

On the VHI, 29 of the 38 patients had an improvement in their overall raw score after treatment. The difference in the overall score change reached statistical significance, with improvement in the posttreatment responses ($p \leq .0003$). The individual categories of functional, physical, and emotional handicaps also demonstrated statistically significant improvement on the posttreatment scores ($p \leq .0005$, $.0001$, and $.0001$, respectively). Twenty-seven of the 38 patients had an improvement in their raw score on the assessment of their functional voice handicap, 32 of the 38 on their physical handicap, and 31 of the 38 on their emotional handicap.

The questions on the SF-36 are separated into 8 different categories designed to measure the subjects' physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning, and mental health. The subjects showed a statistically significant improvement in their perceptions on mental health ($p \leq .03$) after treatment for their SD. When the 3 patients who experienced posttreatment breathy dysphonia for more than 1 month were eliminated, then the perceived improvements in the area of social functioning after treatment also reached statistical significance

COMPARISON OF SF-36 SCORES BETWEEN NORMALS AND PATIENTS WITH SD BEFORE AND AFTER TREATMENT WITH BTX

Domain	US Norms ⁹	SD Patients		Probability		
		Before BTX	After BTX	US Norms vs SD Before BTX	US Norms vs SD After BTX	Change With Treatment
Physical functioning	84.2 ± 23.3	80.8 ± 24.6	83.5 ± 20.2	.4155	.8484	.1988
Physical role functioning	81.0 ± 34.0	66.4 ± 39.7	67.9 ± 37.2	.0371	.0440	.8347
Bodily pain	75.1 ± 23.7	75.6 ± 26.0	79.9 ± 18.6	.8644	.1420	.3654
General health	72.0 ± 20.3	73.6 ± 20.2	69.4 ± 20.3	.6361	.4611	.2159
Vitality	60.9 ± 21.0	55.0 ± 23.3	58.4 ± 23.6	.1427	.5392	.2169
Social functioning	83.3 ± 22.7	63.0 ± 26.5	75.1 ± 28.0	.0001	.1087	.0409
Emotional role functioning	81.3 ± 33.0	67.8 ± 41.7	76.0 ± 34.6	.0642	.3861	.2915
Mental health	74.7 ± 18.0	70.4 ± 18.0	79.2 ± 13.3	.1713	.0525	.0028

SF-36 — Short Form 36-Item Health Survey⁹ (Medical Outcomes Trust, Boston, Mass), SD — spasmodic dysphonia, BTX — botulinum toxin.

($p \leq .04$). The changes in posttreatment scores in the other 6 areas on the SF-36 did not reach statistical significance (see Table⁹).

As compared with US normals, the patients with adductor SD were significantly worse on their ratings of physical role functioning ($p < .0371$) and social functioning ($p < .0001$). After treatment with BTX, the patients remained significantly worse in their perception of physical role functioning ($p \leq .044$), but were no longer significantly worse than US normals on their rating of social functioning ($p \leq .1087$). Evaluation of the other categories did not reveal significant differences (see Table).

DISCUSSION

The VHI appears to be a sensitive indicator of self-perceived changes in vocal function. The responses showed a markedly significant lessening in the perception of functional, physical, and emotional voice handicaps in patients with SD treated with BTX. Of the 9 responders who did not show an improvement in their overall posttreatment scores, a prolonged breathy voice was the reason cited for poor outcome.

At our institution, the starting dose of BTX is 2.5 mouse units injected bilaterally into the TA muscles. This dose results in significant weakening of the laryngeal adductors. Glottal incompetence secondary to vocal fold flaccidity is frequently apparent on endoscopic examination. If the initial dose regimen produces a profound effect with prolonged, troublesome whispering dysphonia, then the dose at the subsequent injections is frequently dropped to 2.5 mouse units injected into only one vocal fold. We have previously demonstrated that alternating low-dose unilateral injections lessens the period of time during which patients consider themselves overtreated and improves the ratio of the well-treated phase to the overtreated phase.¹¹

For the purpose of this study, which was to determine the overall effects of the treatment of SD with BTX on the physical, psychological, and emotional health of patients, only subjects undergoing their first injection were enrolled. In this manner, an unbiased reporting of the pretreatment effects of the disorder could be determined. Unfortunately, with our initial dose regimen, 9 of the 38 patients were in a breathy or overtreated phase for more than 2 weeks. Three of these remained breathy for more than 4 weeks. This outcome negatively influenced their responses on the posttreatment testing. The overall outcomes of treatment may, in the future, demonstrate greater improvement if the prolonged breathy phase can be eliminated, or if outcomes are collected after a longer post-treatment interval.

Evaluation of the responses to the SF-36 showed that the treatment of SD with BTX resulted in patients' perceptions of improvement in their physical functioning, vitality, and emotional role functioning, as well as lessening of their perceptions of bodily pain. These trends did not reach statistical significance. The SF-36 was developed to assess general health. Remarkably, this study demonstrates that although the isolated treatment of voice disorders can produce a perceived improvement in some general health parameters, comorbidities, such as other neurologic disorders, advanced age, arthritis, hypertension, and heart disease, may have a greater or similar impact on perceived health. The responders did report a statistically significant improvement in their mental health and social functioning.

The treated patients experienced less disruption of their social interactions and had an improved mental health outlook. This finding is supported by the comparison of patients with SD before and after treatment to US normal controls, which showed that treated patients no longer rated themselves as significantly different or impaired in their social function-

ing. The cost savings to society remain undetermined, but treated patients may be less likely to be absent from work and may be more productive when present.

CONCLUSIONS

Patients who underwent BTX injection for the treatment of adductor SD experienced a perceived lessening in the voice handicap produced by the disorder. This lessening of the perceived handicap occurred in physical, functional, and emotional voice parameters as measured by the VHI. The posttreat-

ment changes reached statistical significance in all VHI parameters. In addition, these same patients also reported a perceived improvement in their mental health and in their social functioning as measured by the SF-36. These improvements after treatment were statistically significant. Before treatment, patients with adductor SD rated themselves significantly differently from US normals in the areas of physical role functioning and social functioning. Their social functioning improved and normalized after treatment. These data support the continued treatment of patients with SD by the injection of BTX.

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ACOUSTIC, AERODYNAMIC, AND VIDEOSTROBOSCOPIC FEATURES OF BILATERAL VOCAL FOLD LESIONS

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Successful treatment of bilateral vocal fold lesions depends on the accuracy of the diagnosis. For example, the preferred treatment for vocal fold nodules is voice therapy; in contrast, treatment for a unilateral vocal fold lesion with a contralateral reactive vocal fold lesion (UVFL/RL) usually involves phonosurgery and voice therapy. Differentiation between vocal fold nodules and a UVFL/RL is often challenging. The purpose of this study was to facilitate diagnostic accuracy and improve treatment for patients with bilateral vocal fold lesions by attempting to identify distinct features of patients with either vocal fold nodules or a UVFL/RL with acoustic, aerodynamic, stroboscopic, and patient self-perception measures. The objective voice analysis, Voice Handicap Index, and laryngovideostroboscopic examinations of 85 patients with bilateral vocal fold lesions were reviewed. The results indicated that the patients with a UVFL/RL presented a diagnostic profile that was significantly different from that of patients with vocal fold nodules. Statistically significant differences were found for 1) symmetry of vocal fold vibration, 2) amplitude perturbations, 3) estimated subglottic pressure, and 4) Voice Handicap Index. These results suggest that a composite assessment of acoustic, aerodynamic, and videostroboscopic phonatory features facilitates differentiation between patients with vocal fold nodules and those with a UVFL/RL. The improved diagnostic accuracy afforded by multiparametric assessment provides a comprehensive framework for the treatment of these two distinct vocal fold disorders.

KEY WORDS — acoustic analysis, aerodynamic analysis, bilateral vocal fold lesions, reactive vocal fold lesion, videostroboscopy, vocal fold cyst, vocal fold nodule, vocal fold polyp.

INTRODUCTION

A dramatic improvement in the knowledge base regarding voice disorders has occurred over the past 20 years. These improvements have occurred in the arenas of diagnostic testing, knowledge of vocal fold physiology, and understanding of vocal fold cellular and extracellular composition.¹⁻⁴ The advances in vocal fold imaging afforded by laryngovideostroboscopy (LVS) have resulted in an improved ability to accurately diagnose bilateral vocal fold lesions.⁵ However, a common diagnostic dilemma for clinicians is differentiating between patients with vocal fold nodules (Fig 1) and patients with a unilateral vocal fold lesion (cyst or polyp) and a contralateral "reactive vocal fold lesion" (UVFL/RL; Fig 2). This differentiation is particularly important because the treatment of vocal fold nodules is generally voice therapy, whereas treatment for a cyst or polyp with a reactive lesion will often entail phonosurgery in conjunction with voice therapy.⁶⁻⁹

Retrospective analysis of the results of an initial diagnostic assessment protocol was performed for patients with bilateral vocal fold lesions. The goal of this study was to determine whether different diagnostic methods can assist in the differentiation of pa-

tients with these two different types of bilateral vocal fold lesions. With an improved understanding of the differences between these two vocal disorders, the voice clinician's diagnostic power will be en-

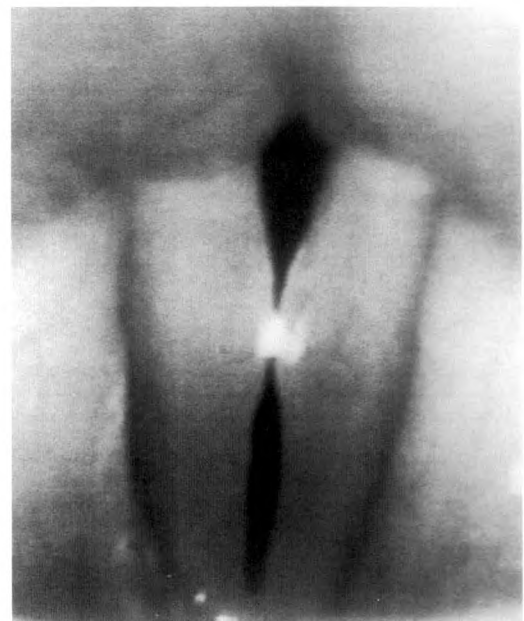


Fig 1. Vocal nodules; bilateral symmetric masses of mid-membranous vocal folds.

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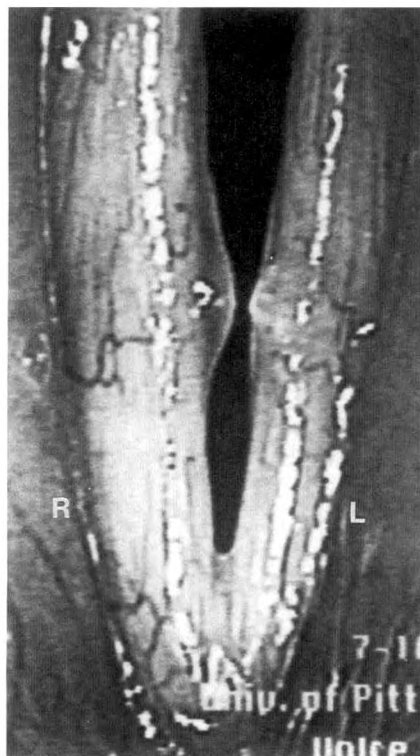


Fig 2. Right vocal fold polyp and left reactive vocal fold lesion. Note asymmetry of lesions.

hanced, and efficient treatment protocols to achieve maximum vocal outcome can be implemented.

Many vocal fold lesions are thought to occur as a result of repeated trauma. A reactive vocal fold lesion opposite a cyst or polyp is also thought to occur as a result of repeated trauma. The reactive vocal fold lesion is usually seen in the mid-portion of the membranous vocal fold, immediately opposite the unilateral vocal fold lesion (Fig 3). The size and morphological features of the reactive vocal fold lesion vary significantly; however, a "cup-and-saucer" shape is often seen on the medial aspect of the reactive vocal fold lesion (Fig 4). This indentation appears to arise

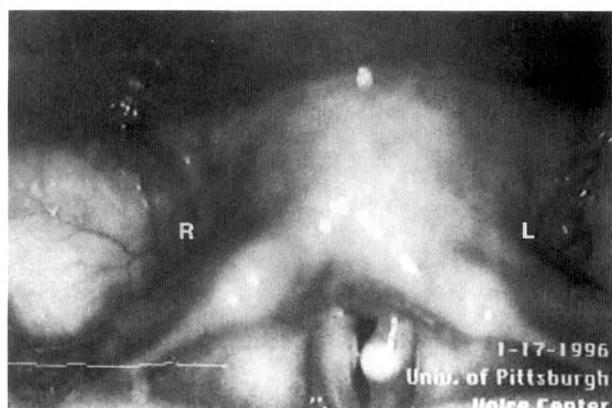


Fig 3. Left vocal fold cyst and right reactive vocal fold lesion. Note elevated "plateau" of reactive lesion on which contralateral vocal fold cyst strikes during phonation.



Fig 4. Left vocal fold cyst and right reactive vocal fold lesion. Note "cup-and-saucer" contour of medial surface of reactive vocal fold lesion.

from the focal trauma caused by the contralateral vocal fold cyst or polyp during vocal fold vibration. Vocal fold nodules, however, generally appear as bilateral, symmetric masses in the mid-membranous vocal fold (Fig 1).

METHODS

We performed a retrospective review of 103 consecutive patients who presented to the University of Pittsburgh Voice Center with bilateral vocal fold lesions. Six patients with a diagnosis of a UVFL/RL who did not undergo surgery were excluded from the analysis (diagnosis not confirmed). Likewise, 4 patients in whom a UVFL/RL was diagnosed but who were lost to follow-up were excluded. All patients underwent a multidisciplinary, comprehensive voice evaluation that included a thorough medical and voice-use history, head and neck examination, medical speech evaluation, objective voice analysis (including acoustic and aerodynamic assessment; Table 1), and LVS examination. In addition, each patient completed the Voice Handicap Index (VHI) before the evaluation. The VHI is a patient self-report instrument that quantifies a patient's perception of disability due to his or her voice.¹⁰ After completion of the above evaluations, a diagnosis was rendered and treatment decisions were individualized on the basis of the findings of the evaluation and the patient's vocal demands. No definitive diagnosis was rendered if a

TABLE 1. VOICE ANALYSIS MEASUREMENTS

Acoustic analysis	
Sustained /a/	
	Average fundamental frequency (F0)
	Phonatory F0 range in semitones
	Jitter percent
	Relative average perturbation
	Shimmer percent
	Peak amplitude variation
	Noise-to-harmonics ratio
Connected speech	
	Average F0
	Highest F0
	Lowest F0
	Standard deviation of F0
	Phonatory F0 range in semitones
Aerodynamic analysis	
/pipi/	
	Mean airflow rate /i/
	Sound pressure level
	Peak air pressure
	Laryngeal airway resistance
Connected speech	
	Mean airflow rate (vocalic segments)
	Sound pressure level
	Peak air pressure
	Laryngeal airway resistance
	Mean flow rate /a/
	Maximum phonation time /a/

patient had apparent bilateral vocal fold lesions in conjunction with laryngitis. Subsequent examination findings were used to make the definitive diagnosis in these instances.

Although treatment was individualized, the patients in whom vocal fold nodules were diagnosed ($N = 29$) were treated with voice therapy, and those with a UVFL/RL ($N = 74$) were offered combined phonomicrosurgery and voice therapy (before and after operation). Sixty-five patients in whom a UVFL/RL was initially diagnosed had their diagnosis confirmed at surgery. One patient was found at surgery to have bilateral hemorrhagic masses, and 1 patient was found to have vocal fold nodules. All but 6 pa-

tients with an initial diagnosis of vocal fold nodules underwent a minimum of 1 follow-up LVS examination after the completion of voice therapy (approximately 10 sessions). Three patients in whom vocal fold nodules were initially diagnosed were found to have a UVFL/RL on follow-up examination (1 surgically confirmed). The study groups include 21 patients with vocal fold nodules and 64 patients with a UVFL/RL (Fig 5).

The voice analysis data were collected from the patients in a sound-treated room. The subjects were seated and fitted with a head-mounted microphone (AKG C410, AKG Acoustics; San Leandro, Calif), with the microphone placed approximately 2 inches (5 cm) from the mouth at a 45° angle from the side of the mouth. Each subject was instructed to produce the vowel /a/ at a comfortable effort level for at least 2 seconds. The sample was stored (Kay Elemetrics CSL, Englewood, NJ) at a sampling rate of 50 kHz. This was followed by reading an all-voiced sentence, "We mow our lawn all year." Each patient was instructed to read the sentence using his or her most comfortable effort level. This all-voiced sample was also captured on the Kay CSL at a sampling rate of 25 kHz.

The data were analyzed on the Kay MDVP (Kay Elemetrics) voice analysis system. For the sustained vowel samples, the initial and final 0.25 seconds were excluded from the analysis to avoid the burst associated with voice onset and the pitch breaks that may occur with termination. For the connected speech analysis, the initial and final 0.25 seconds of each sample were excluded. Acoustic analysis was included in the study only if the patient had a type I voice (quasiperiodic) per the NCVS guidelines for acoustic perturbation analysis.¹¹

Aerodynamic analysis was performed on each subject with the Kay Aerophone (Kay Elemetrics). The subjects were seated comfortably and given time to accommodate to the flow-pressure collection mask. They were asked to repeat the syllable /pi/ at least 8 times in succession at a rate of approximately 1 per second at their comfortable effort level after demon-

Fig 5. Diagnostic categories and follow-up results in 103 patients with bilateral vocal fold lesions.

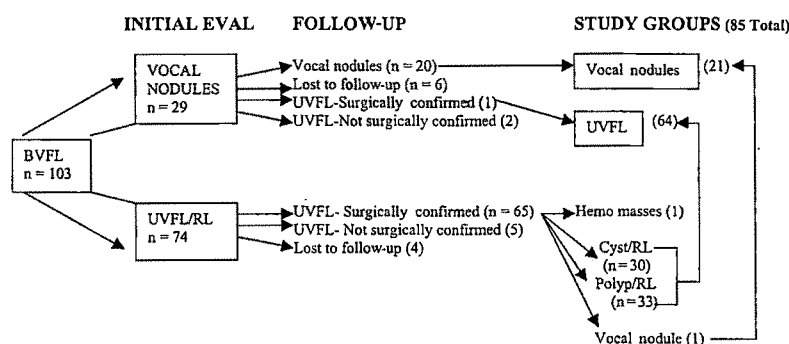


TABLE 2. DEMOGRAPHIC DATA

	Total	Nodules	UVFL/RL
No. of patients	85	21	64
Female	80	19	61
Male	5	2	3
Mean age (y)	30.8	27.4	32.4
Mean duration of symptoms (mo)	26.1	13.6	31.6

UVFL/RL — unilateral vocal fold lesion with contralateral "reaction lesion."

stration. This was followed by producing a sustained /a/ in the Aerophone mask at a comfortable effort level for at least 2 seconds. An experienced voice scientist (L.E.L. or T.M.) analyzed the middle 4 syllable productions to obtain the measures of airflow rate, peak subglottic pressure, vocal intensity, and laryngeal airway resistance. The central 1.5-second segment of the sustained vowel was used to obtain the mean flow rate. Aerodynamic measures were also taken of the speech sample "Pay Paul a penny," collected at the patient's most comfortable effort level.

The LVS examination was done with a variety of phonatory tasks (Kay Elemetrics, RLS 9100) and was done per-oral in the majority of examinations with a 70° rigid telescope. When patient factors precluded rigid laryngoscopy, flexible transnasal laryngoscopy was used for the LVS examination. The phonatory tasks of the LVS included sustained /a/ and /i/ at modal, low, and high pitches. The LVS was performed at several sampling rates and several intensities. The LVS findings at the patient's modal and elevated pitches on a soft, sustained /i/ in the "slow" setting of the laryngovideostroboscope (1 glottal cycle per 2 seconds) were found to be the most indicative of any asymmetric vocal fold vibration.

Each LVS examination was reviewed by the authors in a team format (C.A.R., T.M.), graded on a standardized scoring sheet, and entered into the study database. The LVS findings were discussed after the examination and in conjunction with re-review of the examination videotape in slow motion or frame-by-frame analysis. The features of the LVS examination that were recorded included vocal fold vibration amplitude and phase. These 2 characteristics were noted to be either asymmetric or symmetric. The periodicity of the vocal fold vibration was graded as regular, fairly regular, or irregular. The glottic closure pattern was first scored as complete, incomplete, or incomplete at certain frequency-intensity combinations. If an incomplete glottic closure pattern was identified, it was further described as spindle-, hourglass-, transglottic-, or irregular-shaped. The individual amplitude and mucosal wave behavior of each vocal fold was then graded as normal, decreased, or increased.

The identification and description of any adynamic segments of the vocal folds were also recorded. Vocal fold edge characteristics (smooth, rough, straight, or irregular) were noted bilaterally. Any mass lesions and a presumptive diagnosis were noted on the LVS grading sheet.

Patient voice laboratory data, LVS results, VHI, demographics, and diagnostic category information were entered into a computer spreadsheet (Excel 5.0, Microsoft, Redmond, Wash). The patient data were submitted to statistical testing using the general linear model of the SPSS (SPSS 8.0, SPSS Inc, Chicago, Ill). For each measure, multivariate testing was done with the Wilks' λ test. A χ^2 analysis was performed on the LVS results for mucosal wave amplitude.

Sixty-five of the 74 patients with an initial diagnosis of a UVFL/RL were treated with surgery after preoperative voice therapy. Phonomicrosurgery for the UVFL/RL group was used to confirm the final diagnosis. A mucosal incision was made immediately lateral to each lesion, and a microflap was elevated medially. In all but 2 of the patients who underwent surgery, the submucosal pathological findings of a polyp or cyst were found on the suspected UVFL side, and only epithelial thickening on the RL side. Vocal fold nodules were found at exploration in 1 case, and bilateral hemorrhagic lesions were found in another (Fig 5).

RESULTS

Eighty-five patients were included in the study. Sixty-four patients (75%) had diagnoses of a UVFL/RL, and 21 had diagnoses of vocal fold nodules (Table 2). The majority of the patients were female (94%). A review of the vocal fold pathological and morphological characteristics found on LVS revealed a wide range in the variation of size and shape of the vocal folds of the UVFL/RL group (Figs 1-4). No specific criteria with respect to size and shape could be identified for either the vocal fold nodule group or the UVFL/RL group.

Observation of the mucosal wave behavior of each vocal fold during LVS examination revealed a significant trend toward decreased mucosal wave vibration of the vocal fold with the UVFL in comparison with the contralateral RL vocal fold and the vocal folds with nodules. Significant asymmetric vocal fold vibration was found with LVS in the UVFL/RL patients, especially when compared with the LVS pattern of the patients with vocal fold nodules. The vibratory characteristics of the RL vocal fold were comparable with those seen in patients with vocal fold nodules, ie, minimal reduction of the mucosal wave.

TABLE 3. STATISTICALLY SIGNIFICANT DIFFERENCES BETWEEN PATIENTS WITH VOCAL FOLD NODULES AND PATIENTS WITH UNILATERAL VOCAL FOLD LESION AND REACTIVE LESION

Mean	N	Total	Nodules	UVFL/RL	p	F	df
Voice Handicap Index	77	42.57	25.2	48.7	.001	19.52	1
Shimmer /a/ (%)	68	4.94	3.31 (1.4-8.2)	5.52 (1.2-16.9)	.009	7.34	1
Peak amplitude variation /a/ (%)	68	18.82	12.99 (3.4-32.9)	20.92 (7.4-52.2)	.005	8.58	1
Peak air pressure /pipi/ (cm H ₂ O)	74	8.40	6.91 (3.64-10.5)	9.00 (1.65-31.9)	.042	4.30	1
Peak air pressure speech (cm H ₂ O)	62	8.74	7.58 (3.6-10.5)	9.26 (3.6-19.4)	.045	4.199	1
Sound pressure level /pipi/ (dB)	74	70.9	70.5 (65.2-78)	72.13 (60.5-80.8)	.047	4.205	1

Statistical testing recorded that mucosal wave amplitude findings were different on the UVFL side as compared with the RL vocal fold and vocal folds with nodules. There was no difference in the findings as a group between the RL vocal folds and folds with nodules. Of 64 patients with UVFL/RLs, the mucosal wave amplitude on the UVFL side was increased in 1, normal in 5, and decreased in 8. On the RL side, the amplitude was increased in 3, normal in 51, and decreased in 10. Of 21 patients with nodules, the amplitude was increased in 1, normal in 17, and decreased in 3 on the right side, and increased in 2, normal in 15, and decreased in 4 on the left side.

The VHI showed significant differences between the 2 patient groups ($p = .001$; Table 3). The UVFL/RL group had a higher average VHI score than the vocal fold nodule group. This difference indicates that this group of patients, on average, had a higher self-perception of disability due to their voice disorder. Further analysis revealed similar findings for each subscore of the VHI (functional, physical, and emotional).

The acoustic analysis measures that demonstrated a significant difference between the two diagnostic groups were the measures of shimmer and standard deviation of peak amplitude variation during sustained phonation (Table 3). Fundamental frequency (F₀) and other measures of perturbation were not significantly different between the two groups. None of the acoustic measures of connected speech were different between the two groups. These findings were also true when the male patients were excluded from the analysis to exclude a possible gender-related acoustic signal bias.

The aerodynamic analysis of voice production revealed that peak air pressures were statistically significantly different between the two patient groups. Each task revealed that peak air pressure (estimated subglottic air pressure) was significantly elevated in the UVFL/RL group. This finding was consistent for 2 different phonatory tasks: syllabic production of /pipi/, and a connected speech task ("Pay Paul a penny").

DISCUSSION

Because the optimal treatment for patients with vocal fold nodules and that for patients with a UVFL/RL are different, an accurate diagnosis is the first and most important step to ensuring proper management. The LVS finding of decreased amplitude of the mucosal wave motion for cysts and polyps is consistent with the present understanding of the difference in the histopathology of vocal fold cysts and vocal fold polyps versus vocal fold nodules. The dampening of the mucosal wave has been attributed to the more extensive involvement of a vocal fold cyst or polyp in the subepithelium and the superficial layer of the lamina propria of the vocal fold. We did not find this in patients with vocal fold nodules. In the case of vocal fold nodules, the lesion is thought to be more superficial and therefore may not significantly dampen the mucosal wave.

The acoustic analysis revealed statistically significant increased shimmer and peak amplitude variation in patients with a UVFL/RL compared with patients with vocal fold nodules. This finding is consistent with the working understanding of the increased disruption of normal vocal fold anatomy and physiology associated with a vocal fold cyst or polyp.

No differences between groups were found in the mean F₀ of the vowel /a/ or in the mean speaking F₀ of running speech. The mean F₀ values for both groups of subjects were lower than previously published norms.¹² Thus, regardless of the histopathology, the increased mass of the vocal folds may be the basis for a lower mean F₀. Alternatively, the low F₀ may be associated with a coexistent muscle tension dysphonia (secondary to the glottal incompetence associated with the vocal fold lesions).

Aerodynamic analysis of patients with bilateral vocal fold lesions showed that decreased laryngeal efficiency is found in patients with a UVFL/RL to a greater extent than in patients with vocal fold nodules. This is evidenced by the higher peak air pressure found in the UVFL/RL group as compared with the vocal fold nodule group. These results represent disruption of vocal fold vibration and laryngeal valving efficiency as a result of the UVFL/RL's size, lo-

cation, and nature.

The strong difference in the mean VHI scores between the UVFL/RL and vocal fold nodule groups suggests that the UVFL/RL patients, as a whole, had a higher perception of vocal disability than the vocal fold nodule group. This finding does not mean that the VHI can be used exclusively for diagnostic purposes. The relationship of the VHI to other important patient factors (such as age, duration of symptoms, occupation, diagnosis, and voice laboratory measures) is part of an ongoing research project. Rosen and Murry¹³ found that the mean VHI was elevated in both singers and nonsingers among patients with the diagnosis of vocal fold cyst as compared with patients with vocal fold nodules.

Several case reports describe patients with a UVFL/RL and use the term "reactive nodule" to describe the contralateral vocal fold lesion.^{14,15} In addition, Loire et al¹⁶ reported the diagnostic entity of a UVFL/RL in a large series discussing benign vocal fold lesions. The diagnosis, treatment, and outcome of these groups of patients, however, have not been examined objectively.

The present study demonstrates that high-quality LVS, objective voice analysis, and the VHI can assist voice clinicians in differentiating between vocal fold nodules and a UVFL/RL in patients who present with bilateral vocal fold lesions. Interpretation of the

LVS and objective voice analysis results requires training and experience. No single measure is adequate to make the diagnostic decision, but we found that the LVS finding of significant asymmetric vocal fold vibration in patients with a UVFL/RL was the most powerful single measure.

Other methods that may be useful in the diagnostic process that are not included in this study include reevaluation after modified voice rest and a short course of high-dose steroids. In addition, a trial course of voice therapy may be instituted as a conservative approach even for patients in whom a UVFL/RL is suspected. Common results of trial voice therapy with vocal hygiene in patients with a UVFL/RL are reduced vocal fold edema, reduction or resolution of the contralateral RL, and persistence of the UVFL (assuming patient compliance). This outcome can often be diagnostic, and thus, further treatment (surgery) can be implemented if indicated.

This study found that several parameters can assist voice clinicians in differentiating types of bilateral vocal fold lesions. The VHI, LVS, and objective voice analysis all show differences, in aggregate, between vocal fold nodules and a UVFL/RL. These findings can assist clinicians in the future in differentiating these difficult diagnostic groups, resulting in more accurate and efficient diagnosis and treatment.

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PHOTOGRAPHY OF SEVERE LARYNGEAL OBSTRUCTION

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Thirty-five-millimeter photography using rigid rod lens telescopes at direct laryngoscopy is the most versatile and reliable method of laryngeal documentation. Photography of severe laryngeal obstruction, whether in pediatric or adult patients, mandates a method of anesthesia chosen for maximum patient safety, a laryngoscope selected for optimal exposure, confidence in controlling the airway, and a technique that does not jeopardize the safety of the patient.

KEY WORDS — laryngeal obstruction, larynx, photography.

INTRODUCTION

There are many methods for systematic documentation of laryngeal disease,¹ including a written description, freehand drawing, illustration on a pre-printed diagram, video print, video recording, cine-photography, imaging techniques with ultrasound, x-ray, computed tomography, magnetic resonance imaging, and still photography. Thirty-five-millimeter photography at direct laryngoscopy using rigid telescopes^{2,3} is the most versatile method. Another technique uses an image stored on videotape or minidisk that is selected for printing as a hard-paper color or black-and-white print⁴ and becomes a permanent, static, single-frame record. The quality and color of these prints approaches that of 35-mm photography.⁵ There is an expectation, as technology improves, that digital photography will become more convenient and more widely used, but the clarity and resolution may never surpass those of 35-mm photography. Video recording is the best way to record dynamic changes and to illustrate an operative technique for presentation to a large audience.

Photographic documentation of severe laryngeal obstruction is of vital importance, and 35-mm photography is the most reliable method, as it takes only a short time with the appropriate equipment.

METHOD

Anesthesia. Restoration of the airway in the presence of acute or chronic upper airway obstruction is usually performed with the patient under general anesthesia and is a difficult and demanding responsibility for all involved. General anesthesia for direct endoscopy and photographic documentation always requires close cooperation and understanding be-

tween the otolaryngologist and the anesthesiologist. For the surgical team to be successful, the anesthesiologist must be aware of the instrumentation likely to be used by the endoscopist and be familiar with various alternative procedures that can be used if one approach is inadequate. Likewise, the otolaryngologist needs to be knowledgeable about the principles of anesthesia and the difficulties that may be faced with ventilation. These interdependent fundamentals are crucial when dealing with airway obstruction. Where moderate or severe airway obstruction is present, anesthesia can threaten the safety of the patient, especially in inexperienced hands; the technique must be chosen for maximum patient safety without compromise of diagnostic accuracy.

Equipment for establishing an airway must be always readily available: endotracheal tubes (stiffened with stylet introducers, if necessary), a range of laryngoscopes, ventilating bronchoscopes, a long, large-bore needle suitable for emergency aspiration of an obstructing cyst, and instruments for immediate tracheotomy or cricothyroidotomy.

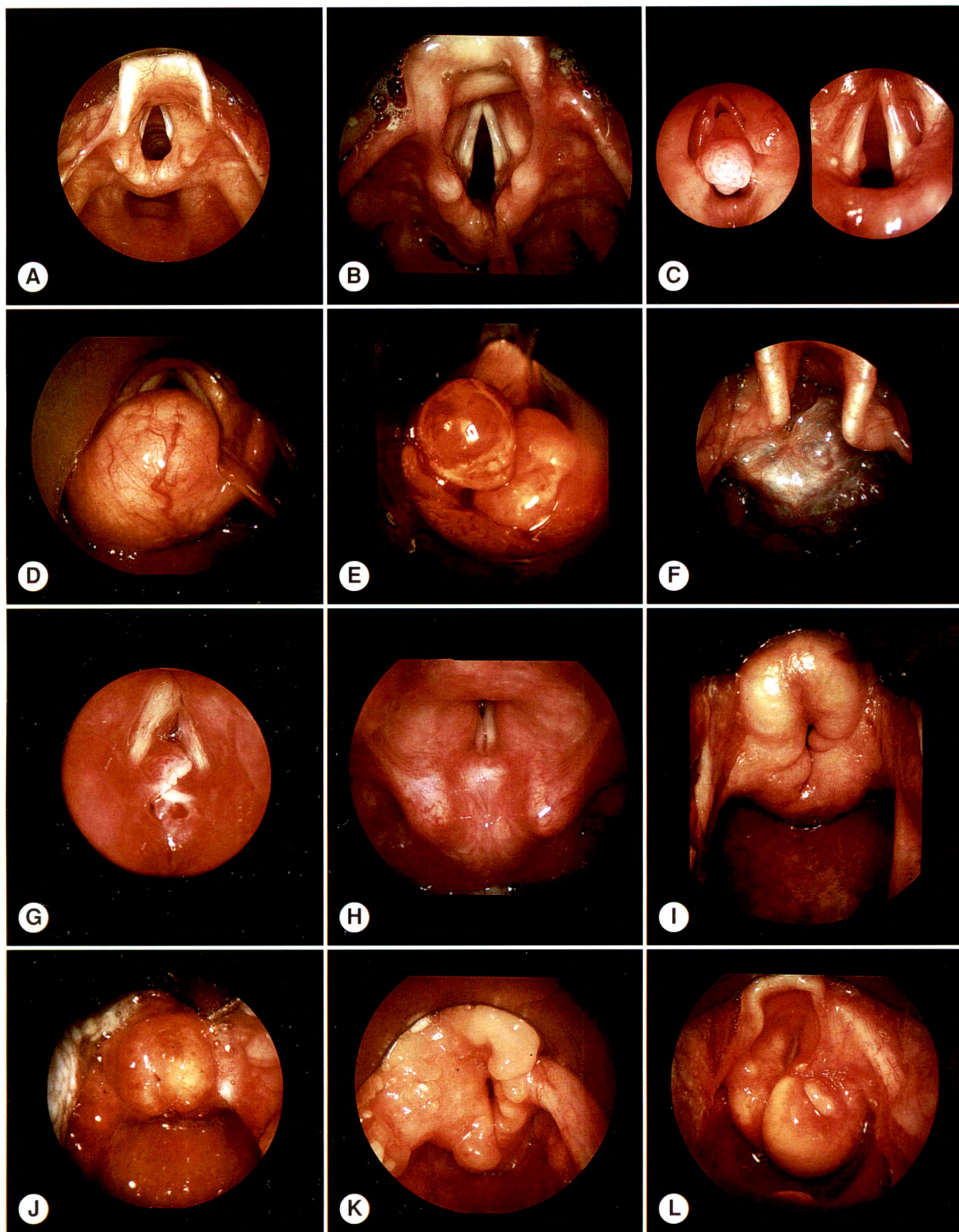
I favor spontaneous respiration anesthesia using a volatile agent such as sevoflurane or halothane in infants and children.⁶ In teenagers and adults,⁷ I prefer muscle paralysis relaxant anesthesia with jet ventilation (either with a proximal metal cannula or with a distal Benjet tube). Topical local anesthesia using lidocaine hydrochloride (up to a maximum of 5 mg/kg of body weight), usually as a 4% solution, is combined with general anesthesia.

Laryngoscopy. The choice of laryngoscope for optimum exposure depends on personal preference. Many designs are available. In adults, I prefer the Lindholm, Kleinsasser, and Benjamin laryngoscopes.

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Photographs taken at direct laryngoscopy. A) Normal infant larynx. B) Normal adult larynx. C) Mass of obstructing papillomas, and glottis 4 weeks after their removal. D) Supraglottic, interarytenoid neurilemoma. E) Bilateral postintubation granulomas. F) Vascular malformation. G) Bilateral postintubation tongues of granulation tissue. H) Rheumatoid arthritis of posterior larynx. I) Sarcoid of larynx. J) Acute epiglottitis. K) Cystic hygroma. L) Benign juvenile xanthogranuloma.

In infants and children (for whom a range of sizes for all ages must be available), I prefer the Karl Storz, Parsons, Benjamin-Lindholm, and Benjamin laryngoscopes. Each of these instruments has a metal cannula for the left-hand side of the laryngoscope for introduction of anesthetic gases. Laryngoscopes with a wide, slotlike opening on the right-hand side are used for endotracheal intubation or passage of a bronchoscope.

Photography. The original Karl Storz equipment for endoscopic photography,^{2,3} designed more than 30 years ago, has been regularly updated. The important components include the following.

1. The lighting unit, which provides not only constant illumination for diagnostic examination, but also momentary brilliant electronic flash for photography.
2. Flexible light-conducting cables.
3. A synchronization cable to connect the hot shoe of the camera to a multipin plug on the lighting unit.
4. A 35-mm single-lens-reflex camera with light metering, motor wind, and a modified, plain, clear, focusing screen.
5. A special zoom lens with variable focal length from 70 to 140 mm.
6. A variety of rigid rod lens telescopes, straight-ahead or angled.

During photography, the camera is held in the right hand, leaving the left free for a handheld laryngoscope or for adjustment of focus or focal length during suspension laryngoscopy. After application of a demisting solution, the telescope is introduced to expose the laryngeal disorder, centering the field for good composition. The shutter is activated to take the photograph, the photographic equipment is with-

drawn, and the diagnostic and operative procedure continues. The time taken for a single photograph is about 10 seconds, but photography should be terminated or not undertaken in the presence of impending life-threatening obstruction.

RESULTS

Examples of photographs of normal airways and conditions causing severe obstruction are shown in the Figure.

DISCUSSION

Causes of upper airway obstruction in adults include both benign and malignant tumors, cysts, bilateral vocal cord paralysis, hemangiomas and vascular malformations, large granulomas, direct injuries to the neck, laryngeal trauma from prolonged intubation, and other causes.

Causes in infants and children include congenital and developmental abnormalities, multiple respiratory papillomas, large cysts, subglottic hemangioma, vascular malformations, cystic hygroma, subglottic stenosis, acute inflammatory upper airway obstruction (croup, acute epiglottitis, diphtheria), and syndromes associated with a difficult airway causing intubation difficulty and airway obstruction.

It is imperative that photography never jeopardize the patient's safety. The opportunity for photography may be momentary, and the laryngologist and the anesthesiologist must remain confident of controlling the airway at all times. The key to safe and successful photography at direct laryngoscopy is to work in concert with a tolerant and cooperative anesthesiologist.

A combination of imaging studies and endoscopic color photography is currently the most practical method of documentation of severe laryngeal obstruction.

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CRITICAL EVALUATION OF NEUROLARYNGOLOGICAL DISORDERS

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Otolaryngological examinations, videostroboscopic image analysis, and laryngeal electromyography were used as a test battery for a critical evaluation in 80 patients. Vocal fold movements were categorized into mobility, restricted mobility, immobility with different positions, and overactive movement. Laryngeal electromyographic examinations were conducted in all patients, and the results were classified into normal, neuropathic, and myopathic patterns. The electromyographic data were integrated with videostroboscopic findings, interpreted with knowledge of biomechanical and electrophysiological mechanisms of the larynx, and correlated clinically with underlying diseases. It is suggested that neurolaryngological procedures are most clinically useful when dictated by a decision-making algorithm.

KEY WORDS — airway protection, laryngeal electromyography, laryngeal physiology, neurolaryngology, phonation, respiration, swallowing.

INTRODUCTION

Knowledge of laryngeal biomechanics¹⁻⁴ and neuroanatomy and neurophysiology⁵⁻¹⁰ has contributed to the development of neurolaryngology as a new branch of otorhinolaryngology. The evaluation of neurolaryngological disorders is clinically challenging, not only because of the complexity of the diseases, but also because of the technical difficulty involved in testing. Consequently, there is a lack of information regarding standard and practical protocols for clinical diagnosis. The emergence of neurolaryngology has drawn great interest from different specialists who work in the fields of voice disorders, swallowing problems, respiratory dysfunction, and many others since the book *Neurolaryngology* was published.¹¹ The framework of neurolaryngology has been enlarged since the First International Neurolaryngology Symposium at the National Institutes of Health in October 1996.

Neurolaryngology is the study of disorders that result from dysfunction of laryngeal sensation and motor control. Neurolaryngology does not merely summarize the contributions of biomechanics, neurology, laryngology, phonology, phonosurgery, and speech-language pathology; rather, it delineates a new interdisciplinary field that studies the neural mechanism of laryngeal functions by means of diverse approaches.¹² As such, neurolaryngology is needed not only to further our understanding of laryngeal diseases, but also to formulate efficacious treatment for many difficult neurolaryngological cases. In recent

years, interest in laryngeal transplantation,^{13,14} laryngeal pacing,¹⁵ laryngeal reconstruction after total laryngectomy,¹⁶ laryngeal nerve anastomosis,¹⁷⁻²¹ and spasmodic dysphonia (SD)^{22,23} has increased with the aid of neurolaryngology. However, the success rate after surgery, the behavioral procedures, and the surgical procedures are still limited, because the details of the mechanisms of laryngeal sensory and neuromotor control are not well known.

Clinically, laryngeal movement dysfunction is common in differential diagnosis. It is critical to evaluate whether the dysfunction is caused by neuronal factors, biomechanical factors, or both. The purpose of our study was to present an algorithm that focused on movement analysis in 80 patients by means of videostrobolaryngoscopic (VSL) investigations to visually clarify movement dysfunction patterns and laryngeal electromyography (LEMG) to electrophysiologically confirm the status of the nerves and muscles. It is hoped that the algorithm will aid diagnosis and selection of treatment methods in patients with laryngeal dysmotility as described elsewhere in the literature. An important point is that the origin of dysmotility, and thus its appropriate treatment, cannot be identified without a combination of clinical (VSL), electrophysiological (LEMG), and, sometimes, radiologic information.

MATERIALS AND METHODS

Subjects and Classification. This study included 80 patients who were referred for neurolaryngologi-

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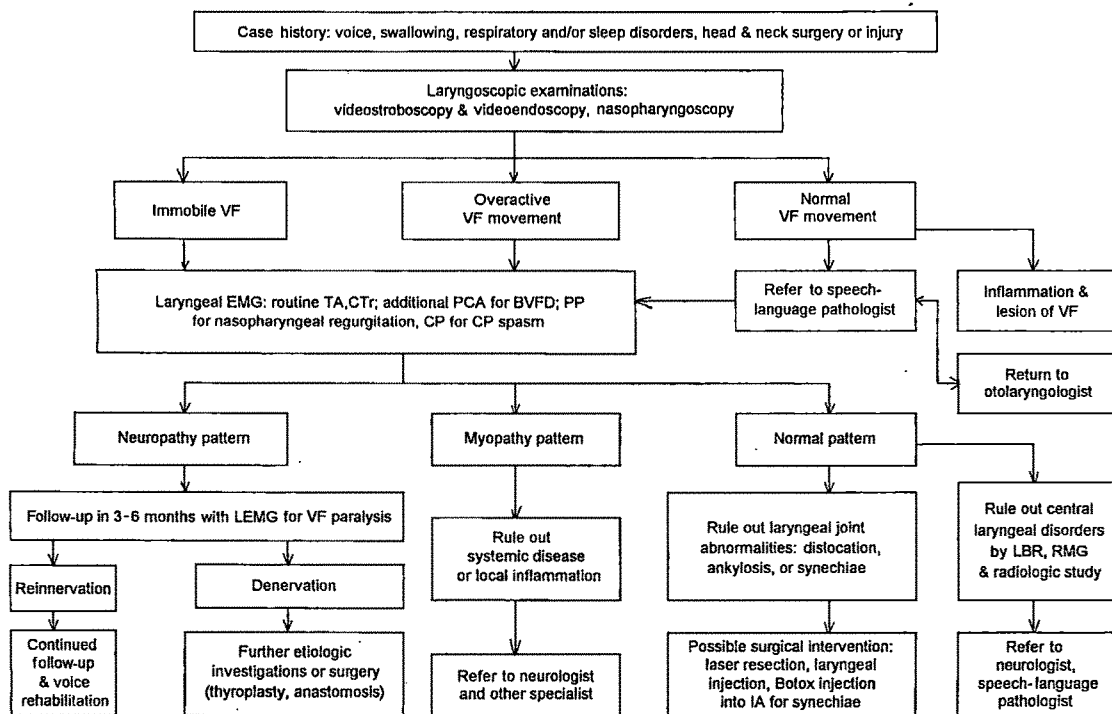


Fig 1. Preferred protocol of evaluation of neurolaryngological disorders. VF — vocal fold, EMG — electromyography, TA — thyroarytenoid muscle, CTr — cricothyroid muscle (pars recta), PCA — posterior cricoarytenoid muscle, BVFD — bilateral vocal fold dysfunction, PP — palatopharyngeal muscle, CP — cricopharyngeal muscle, LEMG — laryngeal EMG, LBR — laryngeal brain stem response, RMG — reflexomyography, IA — interarytenoid muscle.

cal studies for further differential diagnosis. These patients were selected from 1,105 patients who underwent laryngeal videostroboscopy for voice disorders, laryngeal lesions, and/or swallowing problems over a 3-year period at the Department of Otolaryngology–Head and Neck Surgery at Louisiana State University Medical Center in Shreveport. The criteria for inclusion were 1) absence of inflammation and malignant origin; 2) inconsistency between voice and vocal fold (VF) appearance; and 3) failure of conventional treatment (including speech-language therapy) in patients with VF dysfunction. There were 33 men and 47 women, ranging from 1 to 84 years of age. The patients' primary history included dysphonia, dyspnea, and/or dysphagia. Eleven adult subjects with no history of voice or neurologic symptoms or signs also participated in this study as controls. The control group included 8 men and 3 women with a mean age of 24 years (range, 19 to 50 years). After signing the consent form, all participants were examined in our laryngological laboratory.

Videostrobolaryngoscopy. All subjects underwent VSL examination with a Rhino-Larynx Stroboscope (Brüel & Kjær, Denmark), a 70° rigid scope (Brüel & Kjær), a color video camera, and a 17-inch monitor. Fiberoptic flexible nasopharyngoscopy was performed in 7 patients who were hypersensitive to a rigid telescope such that satisfactory images could

not be obtained or who had dysphagia and/or velopharyngeal insufficiency. The images were recorded on a digital tape recorder. The VSL images of VF movement were recorded during quiet respiration, phonation of /i/, and pitch change. In patients with swallowing and velopharyngeal problems, the movements of the soft palate and epiglottis were documented during production of /k/ by means of a flexible endoscope passed through the nasal and nasopharyngeal cavities.

Electrodiagnostic Testing. A Spirit Evoked Potentials System (Nicolet Biomedical Inc, Madison, Wis) was used as the main unit for LEMG recording. Figure 1 illustrates the preferred protocol for a neurolaryngological evaluation routinely used in our clinic. After a detailed history pertinent to neurolaryngological symptoms and head and neck surgery, the patients underwent laryngoscopic examinations including VSL with rigid or flexible endoscopy. The patients who were shown to have laryngeal lesions including tumors or inflammation were returned to otolaryngological management. All patients underwent VSL. The videostroboscopic findings of VF movement were classified into normally mobile, limited mobility, immobile, and overactive movement. The normally mobile VF was defined by the movement range from the midline to the lateral position. The immobile VF was defined as remaining in the same

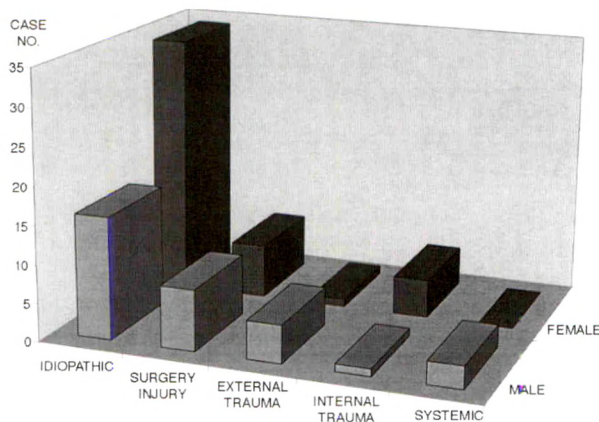


Fig 2. Etiologic mechanisms for 80 patients with laryngeal movement dysfunction who were referred for neurolaryngological evaluation.

position during respiratory and phonatory phases. The positions of immobilized VFs were further categorized into median, paramedian, intermediate, and lateral. Limited movement of the VFs referred to reduced activity or speed in the timing of opening and closing or to reduced lateral excursion of the VFs without an apparent mass lesion. Overactive movement of the VFs was defined as mismatching with phonatory and respiratory phases and persistence in the adducted or abducted position. Such movement was consistent with SD.

The LEMG method was described in our previous studies^{24,25} and has been used as a routine protocol in this clinic. For laryngeal muscle sampling, the amplifier gain was 0.1 mV per division, the filter settings were 100 Hz and 5,000 Hz, and the sweep was set to 5 ms per division. Simultaneous recordings were performed bilaterally with the aid of audible LEMG signals from a loudspeaker. Concentric needle electrodes were selectively used. The basic LEMG battery included evaluation of the 2 major laryngeal muscles: the thyroarytenoid (TA) and the cricothyroid pars recta (CTr). For patients with VF dysfunction but normal recruitment patterns of the TA and CTr muscles, an examination of the posterior cricoarytenoid muscle was performed for additional information. Other laryngeal muscles were selected for sampling depending on the disorder, as discussed below. The patients were in the supine position with a pillow under the shoulders to extend the neck for a full exposure of the cricothyroid space. Anesthetic, 1 to 1.5 mL of 2% Xylocaine, was infiltrated sparingly by subcutaneous injection through the skin over the cricothyroid space. The normal or better-functioning side was routinely sampled first. Electrode verifications were performed before beginning all percutaneous recordings. Patients were instructed to relax and refrain from swallowing during needle electrode insertion and recording.

An LEMG examination was primarily indicated for patients with VF immobility, reduced mobility, or overactive movement of the VFs, as with suspected SD. Some of the patients with a long-term history of voice disorders of unknown causes but who showed normally mobile VFs were also examined by LEMG after consultation with a speech-language pathologist. The TA and CTr muscles were routinely sampled for all patients, with additional sampling of the posterior cricoarytenoid muscle for patients with bilateral VF dysfunction. The palatopharyngeus muscle was sampled in the case of nasopharyngeal regurgitation, and the cricopharyngeus muscle was sampled for cricopharyngeal spasm. The following evaluations and managements were based on our previous study of the major patterns of LEMG.²⁵ If a neuropathic pattern was demonstrated, the patients were classified as having VF paralysis or paresis. These patients were then followed up for 3 to 6 months to monitor for neurapraxia (temporal blocking of impulse transmission), reinnervation (nerve injury with new supply of nerve fibers and recovering function), and denervation (permanent injury). Regular follow-up without surgical intervention was only indicated for patients with reinnervation. Patients with denervation were studied further for etiologic causes or underwent surgery, ie, laryngeal injection, thyroplasty, or nerve anastomosis. For patients with myopathic patterns, systemic diseases and local inflammation were initially ruled out; otherwise, patients were referred to neurologists or other specialists. The combination of intubation history, VF movement dysfunction seen in VSL images, and normal LEMG patterns led to a diagnosis of laryngeal joint abnormalities such as arytenoid dislocation, ankylosis, or synechiae of the posterior commissure. For these patients, surgical interventions were recommended, including laser resection and laryngeal botulinum toxin injection. The patients in this study were managed in the following ways: 1) returned to referring physicians for medical therapy and/or surgery; 2) referred for further neurolaryngological or radiologic assessment; or 3) referred for speech and voice evaluation and/or therapy by speech-language pathologists.

RESULTS

The major causes of 80 cases were categorized and are shown in Fig 2. The major findings in this study are shown in Table 1. Patients whose clinical evaluation indicated SD showed complete closure with tight adduction or overabduction associated with supraglottic activity. By sampling different laryngeal muscles bilaterally, LEMG differentiated the origin or mechanism of neurolaryngological disorders in terms of low versus higher-level laryngeal paralysis,

TABLE 1. RELATIONSHIP OF LARYNGEAL ELECTROMYOGRAPHIC FINDINGS WITH VOCAL FOLD MOVEMENT

Movement	No.	VSL Findings		LEMG Pattern			Total Abnormal
		Bilateral	Unilateral	Normal	Neuropathy	Myopathy	
Immobile							
Median	8	6	2	5	3	0	3
Paramedian	17	2	15	0	15	2	17
Intermediate	7	3	4	1	6	0	6
Lateral	2	1	1	0	2	0	2
Mobile							
Normal	22	22	0	6	11	5	16
Limited	8	2	6	4	1	3	4
Overactive							
Abduction	2	2	0	1	1	0	1
Adduction	14	13	1	0	14	0	14

VSL — videostrobolaryngoscopy, LEMG — laryngeal electromyography.

unilateral versus bilateral peripheral laryngeal paralysis, laryngeal articulation dysfunction, SD, and myopathy. The clinical impressions listed in Table 2 were based on a combination of VSL examination and neurolaryngological findings. Twenty-nine patients were found to have laryngeal nerve lesions, with 23 cases involving the peripheral branches and 6 cases originating from the nerve portion above the nodose ganglion. This study identified 8 cases of neuromuscular disease, including myasthenia gravis. Eleven patients with VF immobility demonstrated a normal pattern of LEMG and were found to have articulation dysfunction (9 cases) or synechia (2 cases). In addition, SD was diagnosed in 24 patients on the basis of the combined criteria of voice struggle, overactive movement of the VFs on VSL, characteristic findings of LEMG, and positive responses to chemodenotomies. Finally, the neurolaryngological findings were normal in 8 patients who were referred for this study. Eleven subjects from the control group underwent LEMG. The results revealed normal patterns in all of these subjects.

DISCUSSION

In general, neurolaryngological disorders are char-

TABLE 2. SUMMARY OF NEUROLARYNGOLOGICAL FINDINGS

Impressions	No.	Unilateral		Bilateral
		Right	Left	
Neural	29			
Peripheral	23	8	13	2
Above nodose ganglion	6	1	2	3
Spasmodic dysphonia	24	0	0	24
Muscular disorders	8	1	2	5
Articulatory injury	9	2	2	5
Synechia	2	0	0	2
Normal	8	0	0	8
Total	80			

acterized mainly by laryngeal motor dysfunction,²⁶ although some involve sensory abnormalities. Many neurolaryngological disorders present complex profiles and are associated with multiple neurologic origins.^{27,28} The evaluation can be frustrating, particularly for diseases of unknown origin. In our study, the recognition of such disorders was initially prompted by laryngological observation of VF motion dysfunction. The literature has shown that the relationship and interaction of phonation, respiration, deglutition, and vocalization is coordinated by the central laryngeal system, particularly by the brain stem.⁷⁻⁹ The position, tension, and movement of the VFs are ultimately determined by laryngeal biomechanics through coordination of joint motion, muscular vectors, and muscular tension. A critical point for our study is that the importance of appropriate application of the neurolaryngological test battery and interpretation of laryngoscopic images or electrodiagnostic findings cannot be overestimated. An algorithmic approach, integrating electrodiagnostic findings with clinical examinations and VSL for the evaluation of neurolaryngological disorders, was applied in this study and is routinely used in our clinic (Fig 1). With this approach, we attempt to evaluate patients with neurolaryngological disorders in time-saving and cost-effective ways.

As already indicated in the literature, the first important step is to rule out malignancy-related VF paralysis or laryngeal movement dysfunction. MacGregor et al²⁹ reported that 21.7% of cases of VF palsy were caused by neoplastic disease (n = 1,308). Our study described 80 patients with VF dysfunction after ruling out tumor compression or invasion as the causal factor in these cases. Dependence on laryngoscopic images of abnormal VF positions, including median, paramedian, intermediate, and lateral, and a deviated glottis as the basis for diagnosis of VF pa-

ralysis or paresis has been challenged by other investigators.^{2,12,30-33} Laryngeal electromyography and other electrodiagnostic tests remain the gold standard for the diagnosis of VF paralysis.³⁴⁻³⁶

In much clinical practice, detailed localization of laryngeal neuropathy is ignored. Clinically, neuropathy in the ipsilateral TA muscle usually indicates unilateral paralysis of the anterior branch of the recurrent laryngeal nerve (RLN). Involvement of both the TA and the posterior cricoarytenoid muscles suggests paralysis of the anterior and posterior branches of the RLN on the ipsilateral side. A neuropathic pattern in the TA and CTr muscles may indicate a lesion to the superior laryngeal nerve and RLN at the level of the nodose ganglion. If neuropathy is demonstrated in the TA and CTr muscles and in the soft palate, the results can be interpreted as indicating a lesion at or above the level of the jugular foramen. Clinical investigations indicate that when a lesion involves the neuron body at or above the nodose ganglion, natural recovery is often incomplete. In our study, the neuropathic pattern was found in 76.47% of patients with an immobile VF and deviated glottis and was compatible with the diagnosis of VF paralysis. In this study, 6 of 34 patients with an immobile VF showed a normal LEMG pattern; this finding suggests that these patients may have laryngeal joint abnormality and are candidates for surgical intervention. A myopathic pattern is an infrequent finding responsible for VF immobility or other abnormal laryngoscopic images. This pattern can be caused by systemic diseases such as systemic lupus erythematosus and myasthenia gravis. Therefore, it may be misleading to depend on the position of the immobile VF for decision-making regarding permanent surgical intervention. Laryngeal brain stem responses and laryngeal reflexomyography have been investigated in humans and animals.³⁷⁻⁴⁴ However, the clinical application of these special examinations remains in preliminary stages. Further study is needed to develop more effective tests for differential diagnosis of central laryngeal disorders, although these may be seen rarely.²⁷ We expect that the integration of neurolaryngological data with radiologic images will provide the most powerful tool in neurolaryngology.

The presence of laryngeal biomechanics in the algorithm emphasizes that intimate linking of the laryngeal joint, ligaments, and muscles is responsible for the fine mechanical movement of the VFs under central laryngeal motor control.¹⁻⁴ In our experience, laryngeal biomechanics should be evaluated with VSL by observing the configuration, speed, and position-

ing of the VFs during a change from respiration to phonation or vice versa, to test the RLN, cricoarytenoid joint, and TA muscle. Changes of the longitudinal axis of the glottis during pitch changes should be observed to assess the function of the superior laryngeal nerve, cricothyroid joint, and CTr muscle. In addition, the movement of the muscular process of the arytenoid cartilage during sneezing should be used to test the function of the cricoarytenoid joint, posterior cricoarytenoid muscles, and interarytenoid (IA) muscles. Such analysis of VSL images allowed us to appropriately select and sample different muscles with LEMG to determine the patient's neuromuscular status and assess possible underlying diseases, and thereby choose an appropriate treatment plan or method.

A final comment regards an extended role of botulinum toxin (Botox) in the treatment of selected neurologic and nonneurologic disorders of the larynx. After confirming the type of VF movements and the status of the laryngeal neuromuscular units with the guidance of the algorithm, we can use Botox injection to modify the biomechanical imbalance of the laryngeal joint-muscle system. First, the Botox injection can inhibit muscular overactivity. For example, an injection of Botox in the TA muscle is effectively used for the treatment of adduction-type SD. Second, temporary paralysis due to Botox injection can enhance the action of the antagonistic muscle. We are the first to propose this procedure in the management of posterior synechiae for a patient with bilateral VF immobility, after ruling out neuropathy. Temporary paralysis of the IA muscle concurrent with posterior synechiae surgery was recommended. The procedure involved an injection of 15 to 20 units of Botox into the IA immediately after laser section of scar tissue. Third, Botox injection may obviate collision between bilateral cartilaginous portions of the VFs, controlling posterior VF granuloma. These procedures also show great potential in the management of cricopharyngeal spasm,³² laryngeal joint dislocation, some paradoxical laryngeal movement, and synkinesis secondary to laryngeal reinnervation.⁴⁵

In summary, the algorithm proposed in this study reflects neurolaryngological and biomechanical principles. The present study adds data and support to the current literature in suggesting that neurolaryngological evaluations are valuable in investigating the mechanism of laryngeal motor control, determining the nature and site of lesion, assessing the efficacy of surgical intervention, and predicting treatment outcome.

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ARGON PLASMA COAGULATION FOR INFERIOR TURBINATE REDUCTION

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Surgical reduction of the inferior turbinate remains a widely used therapy for nasal obstruction caused by hyperplastic turbinates. Current methods are costly and time-consuming, require nasal packing, and cause extended postoperative swelling. Argon plasma coagulation (APC) is a new, innovative technique in otorhinolaryngological surgery that is based on high-frequency electrical current. The current is transmitted through ionized argon gas (plasma) contact-free to the tissue surface and creates a coagulation and devitalization zone with limited penetration. Forty-five patients with nasal obstruction were treated under local anesthesia for reduction of the inferior turbinates with APC. Seventy-six percent of the patients reported an improvement of postoperative swelling within the first week. After 3 months, 86% reported having better nasal airflow than they had before the operation. Macroscopically, after 4 weeks the turbinate was covered by normal mucosa in 51% of the patients. Crust formation was minimal, and no bleeding occurred. Turbinate reduction with APC is an alternative technique with many advantages, and the results are comparable to those of standard techniques. Ninety-five percent of the patients were satisfied with the operation.

KEY WORDS — argon plasma coagulation, nasal obstruction, nasal turbinate.

INTRODUCTION

A wide variety of different techniques for reducing the inferior turbinate are currently in use. The particular choice of technique reflects more the physician's preference and experience than any widely accepted standards. Surgical techniques for the reduction of hyperplastic nasal turbinates that cause obstructed nasal airflow include partial or total reduction of the turbinates by conchotome or scissors, monopolar or bipolar coagulation, inferior turbinate outfracture, and surgery with the Nd:YAG, CO₂, or KTP laser.¹⁻⁸ Each method has its own disadvantages. Some require nasal packing, some are very painful, and some are associated with prolonged postoperative swelling or poor long-term results. Treatment of the hyperplastic inferior turbinate with a new innovative argon plasma coagulation (APC) technique may offer clear benefits. The physical and biological effects of APC on tissue make it likely to be a very efficient technique for this indication.

Argon plasma coagulation, or argon plasma surgery, has been used successfully for more than 20 years for hemostasis of superficial hemorrhages and resection of parenchymatous tissue in open surgery, laparoscopy, and thoracoscopy. Its widespread use followed the report of Farin and Grund⁹ on the effectiveness of APC in thermal destruction of mucosal lesions in the gastrointestinal tract and the tracheobronchial system. Since that time, they have developed special instruments for the endoscopic use of

APC.¹⁰ The method now has a broad range of endoscopic indications. In otorhinolaryngology, we were the first to apply APC, initially for the therapy of juvenile laryngeal papillomatosis with extension into the trachea.^{11,12} Because of its encouraging results, APC has gained significant interest as a new and innovative method; consequently, it has been used for other indications in otolaryngology. Our first clinical experiences with endonasal use of APC showed that it is a useful alternative in the treatment of hereditary hemorrhagic telangiectasia in the nasal mucosa.^{13,14} The aim of the present study was to evaluate the practicability and treatment results of APC used in patients with nasal obstruction caused by hyperplasia of the inferior turbinate.

MATERIAL AND METHODS

Principles of APC Technique. Argon plasma coagulation is based on relatively uncomplicated physical principles. It requires a suitable APC applicator, an argon gas source, and a high-frequency voltage generator. The APC instrument usually consists of a rigid or flexible tube with a ceramic tip. Argon gas flows through this tube and emerges at the distal end, where an electrode serves as one pole of the high-frequency voltage source. The other pole is connected to the patient via a so-called "neutral" electrode, as is usual in electrosurgery. Provided that the high-frequency voltage between the electrode in the APC instrument and the patient is adequate and that the

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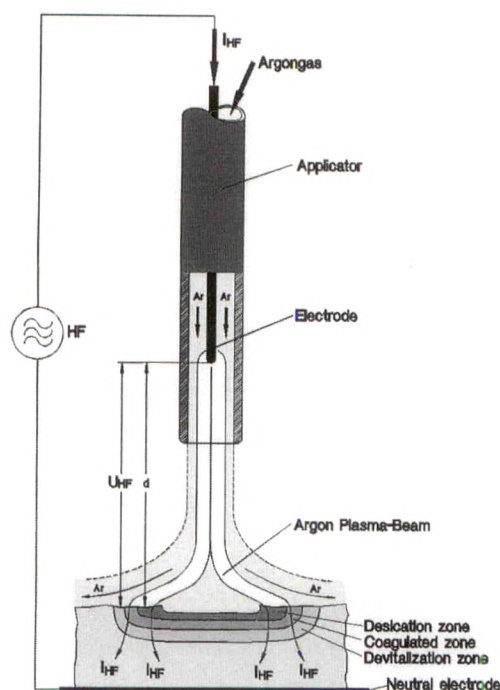


Fig 1. Cross section through argon plasma coagulation (APC) applicator tip with electrode inside and argon gas flow through tube toward tissue surface. Argon gas between applicator tip and tissue is ionized (plasma) by high-frequency voltage, thus enabling plasma to conduct electrical current to tissue surface. (Reprinted with permission.¹³)

distance between the electrode and the tissue of the patient is small enough, the argon ionizes, forming electrically conductive argon plasma in the presence of an electrical field of approximately 500 V/mm, whose strength is expressed in the formula $E = U(HF)/d$, where E is the electrical field, $U(HF)$ is the high-frequency electrical voltage, and d is the distance between the electrode and the tissue. A light blue, luminous beam of argon plasma develops between the electrode and the tissue, and the high-frequency current flows through it and can be applied without direct contact to the tissue (Fig 1¹³).

The argon plasma beam usually seeks out the tissue locations in which the electrical conductivity is the highest. As soon as the electrical conductivity abates at each tissue location because of desiccation, the beam spontaneously moves on to another tissue location, in which electrical conductivity is higher. In this manner, the argon plasma beam stochastically probes the tissue surface in the entire vicinity, resulting in uniformly superficial zones of devitalization, coagulation, and desiccation; ie, the depth of destruction is limited. Because argon gas is inert, APC causes neither carbonization nor vaporization of the tissue — an advantage in the destruction of mucosal lesions, as well as for hemostasis in the upper aerodigestive tract.

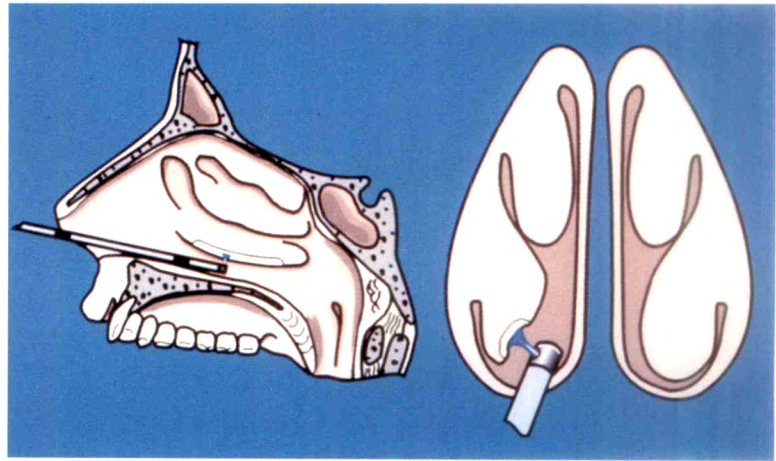
Equipment. Our equipment consists of a generator for high-frequency voltage (ICC 350) and an automatically regulated argon gas supply unit (APC 300) from ERBE Elektromedizin, Tübingen, Germany. For application in the nose, we used a resterilizable, rigid applicator with a ceramic tip and an opening for gas flow at the side of the tip. We set the generator at 40 to 60 W, depending on the desired intensity of effect. The argon gas flow was set at 2.0 L/min.

Patients. We treated 45 patients (17 female, 28 male) with chronic nasal obstruction with APC. Only patients with isolated hyperplastic turbinates and without a clinically relevant deviation of the nasal septum were included. In all cases, hyperplasia of the nasal turbinates was diagnosed rhinoscopically and endoscopically and was subsequently confirmed rhinomanometrically. The mean nasal airflow measured was below 600 mL/s at 150 Pa (mean, 410 ± 85 mL/s) before decongestion in all cases. All patients underwent bilateral reduction of the inferior turbinate with APC. The patients' overall satisfaction with the treatment and the postoperative nasal airflow was assessed after 3 months by a standardized questionnaire that asked the following questions: 1) For how long did crust formation in the nasal cavity last? (1 to 3 days, 4 to 7 days, 7 to 14 days, >14 days); 2) When did you first feel an improvement in nasal obstruction? (1 to 3 days, 4 to 7 days, 7 to 14 days, >14 days, no improvement); 3) Do you feel satisfied with the result of the surgery? (very satisfied, satisfied, dissatisfied); and 4) Would you be willing to undergo the same procedure again? (yes, no).

Technique of Application. The nasal mucosa of the patients was first treated with lidocaine hydrochloride 4% and xylometazoline hydrochloride 0.1%, followed by infiltration with lidocaine hydrochloride 2% and epinephrine concentrated at 1:200,000. Intravenous analgesedation was given on request to fearful patients. A forehead reflector was used for visualization. Only in 8 cases of extensive bulging of the posterior end of the turbinate was 30° endoscopy performed to verify sufficient reduction of tissue after APC application.

Reduction of the turbinate was achieved by passing the APC beam slowly over the lower third to lower half of the inferior turbinate along the entire length of the turbinate to the posterior end (Fig 2¹³). The distance between the surface of the turbinate and the opening of the applicator tip should be between 2 and 8 mm, depending on the available space defined by the anatomic situation. Direct contact of the applicator tip with the turbinate surface should be avoided, because it prevents the desired effects (Fig 3). To prevent the plasma beam from reaching the septal mu-

Fig 2. Technique for turbinate reduction with rigid APC applicator. (Reprinted with permission.¹³)



cosa, a small silicone protective shield was applied to the APC applicator tip. Sufficient application of APC is achieved when the treated mucosal surface has a golden-brown, crusty appearance together with a slight shrinkage of the turbinate.

Postoperative Treatment. No nasal packing was required. The nasal cavity was filled with an ointment containing epinephrine 0.1% (Suprarenin). The patient was asked to use soothing ointment daily (containing dexpanthenol, pantolactone, paraffin, Vaseline). No suction cleaning of the nose was carried out, so as to preserve the fibrin layers on the mucosa. One week after the operation, a careful cleaning of the nasal cavity was carried out. Clinical examinations were performed regularly for the first 2 weeks, and then at 4 and 12 weeks.

RESULTS

During and after the APC treatment, no bleeding occurred; therefore, no nasal packing was required. In the first postoperative week, the treated turbinates showed fibrin layers; they dissolved in the second week. Usually, at the first visit, no crust formation

was seen, because no suction cleaning of the nose had been performed. After the second week, fibrin layers and slight crust formation were seen only rarely. This crust formation is caused by the shedding of the fibrin layers and the underlying granulation tissue. After 4 weeks, 23 of 45 patients (51%) had a macroscopically regenerated mucosa and presented focal patches of whitish discoloration. The other 22 patients (49%) still had some slight granulation tissue on the turbinate surface, but no crusts or fibrin layers. The rhinomanometric studies of all patients after 3 months showed an average total airflow of 815 ± 109 mL/s at 150 Pa before decongestion.

Evaluation of the questionnaires revealed that after operation all patients subjectively had a marked nasal obstruction, which was confirmed rhinoscopically by swollen and partially fibrin-covered turbinates. Seventy-six percent of patients reported that an improvement in nasal patency occurred within 4 to 7 days. After 3 months, 86% of the patients reported that the nasal airflow was improved as compared with the preoperative situation.

Fifty-eight percent were "very satisfied" with the operation, and 37% were "satisfied." The percentage of patients who said they would be willing to undergo the same operation again was 87.5%. One patient was dissatisfied and complained of severe discomfort during the operation. Slight crust formation after 2 weeks was reported by only 16%. No bleeding occurred after the operation. No synechiae were observed. The activation time and energy setting varied according to the degree of hyperplasia and size. The mean activation time for APC in each patient was between 12 and 16 seconds for both sides (see Table).

DISCUSSION

Introducing a new method for turbinate reduction in patients with nasal obstruction is only advisable if the innovation offers advantages over the established

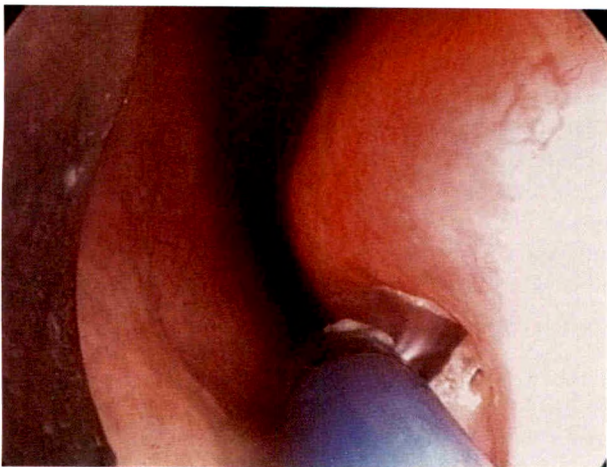


Fig 3. Inferior turbinate with APC applicator tip during treatment.

APPLICATION DATA FOR INFERIOR TURBINATE SURGERY WITH APC FOR 45 PATIENTS

<i>n</i>	<i>Energy Setting (W)*</i>	<i>Cumulative Amount of Argon Gas Used (L)*</i>	<i>Cumulative Time of Action (s)*</i>
15	40	0.6	16
21	50	0.45	13
9	60	0.4	12

*Mean for each energy-setting group.

methods. The aim of the present study was to evaluate the practicability and treatment results of the APC technique. We found that the advantages of APC in the reduction of hyperplastic nasal turbinates are as follows: limited depth of thermal effects; no precaution requirements; simple surgical procedure; accurate application of energy dosage; reduced postsurgical swelling; no bleeding and hence no requirement for (frequently painful) nasal packing^{15,16}; low cost compared with other treatment forms; noncontact application; and good intraoperative visual control of tissue effects. The cost of APC turbinate reduction in comparison with the other techniques is lower, because 1) the investment for the equipment is about one third the cost of a laser unit; 2) argon gas is very cheap (approximately \$1/L); 3) the applicator tip can be used multiple times; 4) no nasal packing is required; 5) no laborious protection of the patient or the equipment is required; and 6) the procedure does not take long to perform.

Reduction of hyperplastic nasal turbinates is frequently carried out with an Nd:YAG or CO₂ laser.¹⁶ As with APC, this procedure can be performed with local anesthesia and without postsurgical nasal packing. However, APC makes it possible to dispense with the precautions required in laser surgery for the patient and the staff of the operating room.

As our study shows, APC has been found to result in a much faster abatement of postsurgical swelling than Nd:YAG therapy, after which the swelling can last up to 3 weeks; this is confirmed by subjective assessment by the patients. The aim of Nd:YAG therapy is to preserve the mucosa by using the laser in a noncontact mode and penetrating into deeper turbinate tissue. The reactive edema diminishes very slowly, and the scarring process, which is finally responsible for a diminished swelling of the turbinate, can be in progress for a month.¹⁷ Moreover, its deep thermal effects are difficult to control, because they depend on the distance of application of the laser probe. Unlike those of the laser, the effects of APC are independent of the distance of the probe from the tissue surface to a certain extent, provided that it does not exceed the maximum distance required for ion-

ization. Even with prolonged application on a confined area, penetration rarely exceeds a certain depth, which basically depends on the power setting. Instead of causing deep thermal effects in the turbinate, as the laser does, APC causes a superficial devitalization (1 to 3 mm).

Surgery on the turbinate with the CO₂ laser is based on a different treatment concept. Because the penetration depth of the CO₂ laser is limited, it is necessary to vaporize tissue to "burn" small pinpoint holes in the head of the inferior turbinate. Success rates (85.9% after 6 months) and patients' opinions about the efficacy of the treatment are higher with CO₂ laser surgery than with Nd:YAG laser surgery (65% after 6 months).¹⁸ The limited penetration depth of the CO₂ laser and the consequent faster reestablishment of patency after surgery are responsible for the better acceptance by the patients. But the posterior parts of the inferior turbinates are difficult to reach with the CO₂ laser. Therefore, the use of the CO₂ laser is limited to selected patients in whom the obstruction is in the anterior parts of the turbinates. Also with limited penetration depth, APC has an 86% success rate after 3 months in terms of improved patency. Overall, 95% of patients reported that they were either satisfied or very satisfied.

There are 2 effects that cause the diminished swelling of the turbinates after APC surgery: first, the immediate APC effect of coagulation and devitalization, and second, a slight submucosal fibrosis. Microscopic studies of the postoperative mucosa are still under way, but preliminary results show that the cilia of the mucosa are present again after 6 weeks. However, long-term study (>3 months) will be necessary, and the success rates may change.

In inexperienced hands, APC is not only safer, because of its limited depth of action, but also easier to handle, because of its variable beam direction, with which the posterior end of the turbinate can be reached easily. Like the Nd:YAG laser, APC is not capable of effectively treating bony hypertrophy of the nasal turbinate. In these cases, only mechanical reduction with scissors or outfracture is effective. Mechanical reduction of the turbinate by scissors leads to a faster improvement of the nasal airflow, but at the cost of bleeding, nasal packing, and significant crust formation.

A further advantage of APC is that there is no carbonization (because argon is chemically inert) or vaporization of tissue, so that crust buildup on the mucosa is reduced during the recovery period. Compared with other techniques, crust formation after APC treatment is far less, because of less bleeding and less tis-

sue destruction. The absence of vaporization in APC therapy also eliminates the possibility of inhalational contamination on the part of the surgeon, which has become of increasing concern. Because of the good visibility of the argon flow at the probe tip, a good control of the effects and the manipulations is ensured.

However, a comparison of APC's advantages with

those of laser surgery and other methods used to reduce the nasal turbinates makes it obvious that APC should be seen as a significant addition or a good alternative to previously used techniques. Our study should be understood as a preliminary investigation. A prospective study of this interesting technique, randomizing sides to compare APC with conventional forms of treatment, is a topic for further investigation.

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POSTOPERATIVE RADIOTHERAPY IN PATIENTS WITH POSITIVE NODES AFTER FUNCTIONAL NECK DISSECTION

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A study was designed to assess the usefulness of postoperative radiotherapy (RT) in patients with surgically treated laryngeal and hypopharyngeal cancer with histologically proven positive neck nodes. Patients underwent operation between 1984 and 1995, with functional neck dissection (FND) being part of the treatment in all cases. The selection criteria included squamous cell carcinoma, negative margins for the primary tumor, and no previous treatment. For evaluation purposes, patients were divided into 2 groups: surgery alone versus surgery with postoperative RT. Eighty-three patients fulfilled the inclusion criteria and entered the study. All but 1 of the patients were men. The mean age was 58 years (range, 35 to 77 years). A multivariate analysis was used to analyze the prognostic parameters selected by univariate analysis, eg, age, alcohol, tumor location, T and N stages, and presence or absence of extracapsular spread and a desmoplastic pattern. Postoperative RT was not selected by univariate analysis as a prognostic factor, but was included in the multivariate analysis in order to assess its impact on survival and recurrence rates. Using the statistical method of multivariate analysis, we could not find evidence of a benefit to survival or local recurrence rates with postoperative RT in this series. Patients younger than 55 years and those with extracapsular spread had a decreased survival rate and a higher neck recurrence rate, irrespective of the treatment method.

KEY WORDS — functional neck dissection, laryngeal cancer, lymph nodes, postoperative radiotherapy, prognosis.

INTRODUCTION

Treatment of most primary cancers of the head and neck should include the neck, as well as the primary site. Cervical metastases are a certain risk factor and constitute the best prognostic indicator in patients with head and neck tumors. The best treatment for the neck in these subjects remains controversial.¹

In Spain, surgery is the most frequent treatment for head and neck tumors. However, the results of treatment in patients with primary tumors of the larynx and hypopharynx and pathologically positive nodes are disappointing. This is especially true when extracapsular spread (ECS) or a desmoplastic pattern is detected in the neck dissection specimen.²⁻⁷ To improve prognosis in patients with pathologically positive neck nodes (pN+ patients), postoperative radiotherapy (RT) is frequently used.

The main goal of this study was to assess the usefulness of postoperative RT in pN+ laryngeal and hypopharyngeal cancer patients.

MATERIALS AND METHODS

Between February 1984 and August 1995, more than 600 patients with malignant neoplasms of the

larynx and hypopharynx were surgically treated at the Department of Otolaryngology of "La Paz" University Hospital. To enter the study, the patients had to fulfill the selection criteria included in Table 1.

Functional neck dissection (FND) was described in the early 1960s by Oswaldo Suárez,⁸ and it is based on fascial compartmentalization of the neck. In the American literature, it has been wrongly associated with a comprehensive type of neck dissection, when the reality is that FND is a conceptual approach to the neck that uses fascial dissection to remove the lymphatic tissue of the neck while preserving important cervical structures. The surgical technique for FND has been thoroughly described in the literature^{9,10} and will not be repeated here. Basically, what the authors use for laryngeal and hypopharyngeal cancer is referred to in the American literature as a selective neck dissection, because the lymph nodes in

TABLE 1. SELECTION CRITERIA FOR INCLUSION IN STUDY

Nc previous treatment
Squamous cell carcinoma
Functional neck dissection
Pathologically proven lymph node metastasis
Negative margins at primary site

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TABLE 2. CLINICAL VARIABLES INCLUDED IN STUDY

Age
Sex
Tobacco
Alcohol
Onset of symptoms (mo)
Location
T
N
M
Surgery for primary tumor
Macroscopic appearance
Number of isolated nodes
Number of positive nodes
Number of nodes with extracapsular spread
Number of nodes with desmoplasia
Local recurrence
Neck recurrence
Distant recurrence
Months until recurrence
Months of survival
Postoperative radiotherapy

area I are routinely spared. Nodal regions II through V are systematically removed with the operation performed by the authors for cancer of the larynx and hypopharynx.

We perform FND in clinically N0 patients and those with palpable mobile nodes. In our department, postoperative RT was administered to all patients with histologically positive nodes until 1990. Since 1991, postoperative RT has been used on a more selective basis. Since January 1991, patients treated with FND have received postoperative RT only when positive or unsatisfactory surgical margins are found after histologic study of the surgical specimen from the primary tumor. No postoperative RT is currently used in FND patients for nodal reasons. However, patients who require radical neck dissection for extensive neck disease undergo postoperative RT as part of their treatment.

This study compares the results of pN+ patients with cancer of the larynx and hypopharynx treated

TABLE 4. RECURRENCE SITES IN ALL PATIENTS

No recurrence	50
Local recurrence	11
Regional recurrence with local control	17
Distant metastasis with local and regional control	5

with FND and postoperative RT (before January 1991) with those of pN+ patients with cancer of the larynx and hypopharynx treated with FND alone (after January 1991). To avoid selection bias, we excluded patients who underwent postoperative RT after December 31, 1990, because they represent a selected group of pN+ patients with an unfavorable prognosis (positive margins at the primary site).

Overall, 83 patients fulfilled the selection criteria and were included in the study. All patients had a minimum follow-up of 30 months or until death. Survival and neck recurrence were statistically analyzed in relation to the variables detailed in Table 2.

The 1988 American Joint Committee TNM classification was used for staging.¹¹ The preoperative distribution of patients according to T and N stages is given in Table 3. All clinically N+ patients had palpable mobile nodes that were not fixed to neck structures at surgery. The N2a and N3 patients included in this series had clinically large nodal masses formed by a conglomerate of lymph nodes. In all cases, the histopathologic study revealed individual nodes smaller than 2.5 cm. The N2b and N2c patients had multiple nodes smaller than 2.5 cm. The specimens of the neck dissections were retrospectively evaluated by a pathologist (D.H.) who had no knowledge of the patient's clinical course. All neck lymph node specimens were classified into 2 categories according to ECS: no ECS (neck metastasis confined within the lymph nodes) and ECS (tumor involving extracapsular surrounding tissue). They were also classified into 2 categories according to dysplasia: no desmoplastic pattern (no fibroblastic reaction of the lymph node to metastatic tumor) and desmoplastic pattern (connective tissue reaction within the node).

For patients who underwent postoperative RT, a

TABLE 3. PREOPERATIVE STAGING

	N0*		N1		N2a		N2b		N2c		N3		Total
	RT	SA	RT	SA	RT	SA	RT	SA	RT	SA	RT	SA	
T1	1	2	1	0	0	0	0	0	0	0	0	0	4
T2	10	4	3	0	0	1	1	2	0	2	0	0	23
T3	12	4	7	2	2	1	0	0	0	4	0	1	33
T4	3	3	3	3	1	1	1	2	4	1	1	0	23
Total	26	13	14	5	3	3	2	4	4	7	1	1	83

RT — patients in radiotherapy group, SA — patients in surgery-alone group.

*Clinically N0 but pathologically N+.

TABLE 5. LIST OF RECURRENCE SITES IN BOTH GROUPS

Group	Local				Regional		Distant
	L	L + R	L + D	L + R + D	R	R + D	D
Surgery + postoperative RT	7	1	0	0	6	2	4
Surgery alone	1	2	0	0	8	1	1

L — local, R — regional, D — distant.

total dose of 60 Gy was delivered at 2 Gy/d on a 5-d/wk schedule, over 6 weeks.

The data were statistically studied on an Inves Pentium computer with the BMDP statistical package (Statistical Software, 1993). The comparison among survival curves and curves of neck recurrence was made by means of the Mantel-Cox (log-rank) test. All statistical tests received the same level of significance of .05.

RESULTS

The mean age was 58 years (range, 35 to 77 years). All but 1 of the patients were men. Fifty patients underwent postoperative RT, and the remaining 33 did not; from a statistical standpoint, the groups were comparable. No significant difference was found in age, sex, staging, surgical technique, or nodal factors between the 2 groups.

The median survival was 83 months after the date of neck dissection. The recurrence sites are detailed in Tables 4 and 5. In the group of irradiated patients, 24 (48%) are alive, 21 (42%) died of the tumor, and 5 (10%) died of other causes. Patients without postoperative RT did very similarly. Sixteen (48.5%) are alive, 11 (33.3%) patients died of their cancer, and 6 (18.2%) died of unrelated causes.

A univariate analysis selected age, alcohol, tumor location, T, N, ECS, and desmoplastic pattern as risk factors for neck recurrence. The same variables, except for alcohol intake, were selected in the study of survival. These variables and postoperative RT were included in the multivariate analysis (Tables 6 and 7).

According to the results of the statistical study, postoperative RT did not improve the rate of survival or decrease the risk of neck recurrence (Tables 6 and 7). However, an age of younger than 55 years and nodes with ECS were selected as having great impact on survival and regional recurrence.

DISCUSSION

Even after complete surgical resection of all macroscopic tumor, many head and neck cancer patients suffer recurrence in the local-regional area. Several factors may be involved.

Differences in tumor aggressiveness or host immunosurveillance may explain the differences among individuals in terms of failure to contain tumor spread, but we still have no tools to measure this. An unrecognized extension of tumor beyond the area of resection could also explain the development of late recurrences.

For many years, postoperative RT within the first 6 weeks after surgery has been considered the standard approach to all pN+ patients surgically treated for squamous cell carcinoma of the head and neck. This approach has been especially recommended for unfavorable cases.^{12,13} However, several authors have not been able to demonstrate a survival benefit resulting from the combined approach,¹⁴⁻¹⁶ whereas others reported an increased local control rate with surgery and postoperative RT in advanced head and neck cancer patients.¹⁷ In these reports, the concept of advanced disease in the neck is a confusing term, because a high percentage of the patients included in the studies were N0. Finally, in some series, the com-

TABLE 6. STATISTICAL STUDY OF SURVIVAL

Parameter	Contrast	Univariate p	p	Multivariate AHR	95% CI	2.5-Year Recurrence-free Survival (%)
Age	≤55 vs >55 years	.0126	.0046	3.0341	1.41-6.54	43.3 vs 71.1
Location	Laryngeal vs hypopharyngeal	.0046	.3677			70.1 vs 28.6
T	T1/T2 vs T3/T4	.0532	.6001			80.6 vs 52.3
N	N0 vs N1/N2a vs N2b/N2c/N3	.0753	.2424			67.5 vs 72.4 vs 32.3
ECS	Yes vs no	.0000	.0000	6.2449	2.70-14.45	30.2 vs 81.5
Desmoplasia	Yes vs no	.0327	.2807			53.8 vs 86.5
Postoperative RT	Yes vs no	.4836	.5349			59.4 vs 64.1

AHR — adjusted hazard ratio, ECS — extracapsular spread, RT — radiotherapy.

TABLE 7. STATISTICAL STUDY OF RECURRENCE

Parameter	Contrast	Univariate <i>p</i>	<i>p</i>	Multivariate AHR	95% CI	2.5-Year Recurrence-free Survival (%)
Age	≤55 vs >55 years	.0014	.0004	3.9201	1.85-8.34	37.1 vs 72.4
Alcohol	Yes vs no	.0726	.1758			54.1 vs 71.5
Location	Laryngeal vs hypopharyngeal	.0025	.4959			68.9 vs 24.6
T	T1/T2 vs T3/T4	.0240	.4983			80.8 vs 50.0
N	N0 vs N1/N2a vs N2b/N2c/N3	.2770	.8951			65.8 vs 68.1 vs 37.1
ECS	Yes vs no	.0000	.0000	5.6031	2.51-12.51	24.4 vs 79.9
Desmoplasia	Yes vs no	.0274	.1501			49.8 vs 87.1
Postoperative RT	Yes vs no	.5476	.7318			58.6 vs 57.1

AHR — adjusted hazard ratio, ECS — extracapsular spread, RT — radiotherapy.

bined approach seemed to improve not only locoregional control, but also the adjusted survival rate for patients with ECS and/or positive margins.¹³

Patients with unfavorable nodal prognostic factors constitute a subgroup of the pN+ population that may require a more aggressive approach than the rest of the pN+ patients. However, the main purpose of this paper was to assess the usefulness of routine postoperative RT after FND in the overall pN+ population. The issue of ECS and other nodal risk factors has been previously addressed by the authors, who could not find a significant benefit from the combined approach in this subgroup of patients in comparison to surgery alone.⁷

We are aware that the main drawback of our study is that it is a retrospective analysis. However, the TNM staging for both groups was comparable, and no statistical difference was found in the distribution of tumor sites and neck metastases in the RT and non-RT groups (Table 5). On the other hand, the prevailing use of postoperative RT in pN+ patients relies on retrospective reports.¹⁸⁻²⁰

Two uncontrolled and uncontrollable key factors are involved in studies comparing surgery versus combined therapy: the quality of surgery and the quality of RT. Whereas the quality of surgery depends mainly on the personal ability of the surgeon, the quality of RT relies on both personal and technological factors. Even accepting the same level of excellence for both the surgeon and the radiotherapist, radiotherapy involves a costly infrastructure that changes very quickly and may differ among institutions. The quality of

RT may contribute to explaining some of the frequent discrepancies in the literature.

Likewise, the subtle modifications introduced over the years in most surgical techniques may be crucial to understanding differences in results from various institutions. This is especially important in retrospective studies in which results are compared over time. In this respect, FND as performed by the authors has a unique consistency over time. The operation was introduced in our Department 30 years ago directly from the experience of Suárez,⁸ and has not experienced substantial changes since then.

The results from this study failed to demonstrate that postoperative RT has a positive impact on neck recurrence or survival in patients with cancer of the larynx and hypopharynx with histologically positive neck nodes surgically treated with FND. It seems that factors other than tumor-related variables may play a significant role in what we call tumor aggressiveness. A better knowledge of cancer immunosurveillance and host-tumor interaction holds the clue to further developments in head and neck cancer treatment. Meanwhile, conventional therapeutic tools will only yield conventional results.

CONCLUSION

Postoperative RT did not show a beneficial effect on survival or neck recurrence in laryngeal and hypopharyngeal cancer patients with positive neck nodes surgically treated with FND. In order to assess the value of other adjuvant treatments in these clinical situations, further studies are required.

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FACIAL NERVE: VASCULAR-RELATED ANATOMY AT THE STYLOMASTOID FORAMEN

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We dissected 30 facial nerves in fresh cadavers after arterial casting with red latex to provide specific information about the arterial-related anatomy of the trunk of the facial nerve from the stylomastoid foramen to its bifurcation. We found that a wide anatomic variability does exist. The trunk of the facial nerve was in proximity to the stylomastoid artery, which originated from the posterior auricular artery in 70% of the specimens (21/30), from the occipital artery in 20% (6/30), and directly from the external carotid artery in 10% (3/30). The stylomastoid artery passed medially to the trunk of the facial nerve in 63 of the specimens (19/30) and laterally in 37% (11/30). Among these 11 specimens, 8 were large-caliber stylomastoid arteries. During parotid surgery, the main trunk of the facial nerve may be difficult to identify, because a large-caliber stylomastoid artery can mask it. Therefore, it is important to dissect this artery with caution.

KEY WORDS — anatomy, facial nerve, stylomastoid artery, stylomastoid foramen.

INTRODUCTION

In parotid surgery, preservation of the facial nerve is a major concern for any surgeon. The facial deformity and ocular complications caused by facial nerve injury are naturally distressing to the patient. Preservation of this nerve depends on a thorough knowledge of its anatomic relationship with the mastoid tip tissues¹ and of the vascular-related anatomy of its trunk. Beahrs and Adson,² in 1958, were the first to note the importance of the posterior auricular artery. Later, Minatogawa et al³ noted the intimate relationship between the trunk of the facial nerve and the stylomastoid artery, but did not specify the origin of this artery. We performed 30 parotid dissections to identify the characteristics of the arterial-related anatomy of the trunk of the facial nerve from the stylomastoid foramen to its bifurcation.

MATERIALS AND METHODS

This study was performed in 15 fresh, nonembalmed adult cadavers (10 men, 5 women). The facial nerve dissections were performed bilaterally, yielding 30 facial nerve studies. In each case, the cause of death was unknown, but none of the subjects had undergone parotid surgery. The parotid dissection was performed systematically after arterial casting with red latex, as outlined below.

Two transverse cutaneous incisions were made, the upper one linking the upper sides of the left and

right sternoclavicular joints, and the lower linking the left and right seventh costal cartilages. One medium vertical cutaneous incision linked the 2 preceding incisions. We thus delimited 2 reclined cutaneous straps. We disjuncted the 2 clavicles, cut the right and left costal cartilages, and proceeded with the ablation of the sternum. The aorta was dissected, and the ascending and descending aortas were ligated. The aortic arch was then catheterized and injected with 200 mL of red latex. This technique enabled us to dye all head and neck vasculature.

Dissection was performed 3 days after latex solidification. A standard parotidectomy incision was started in the preauricular skin crease and curved around the lobule of the ear anteriorly, along an upper neck skin crease. The skin incision was completed, remaining superficial to the platysma. The posterior skin flap was similarly elevated, exposing the cartilaginous portion of the auditory canal, the tip of the mastoid process, and the anterior border of the sternomastoid muscle. The fascia over the anterior border of the sternomastoid muscle was incised, and dissection was started in a plane deep to the tail of the parotid gland, which was retracted anteriorly. Dissection then proceeded anteriorly, lifting off the parotid gland by separating it from the sternomastoid muscle until the posterior belly of the digastric muscle was exposed. The main trunk of the facial nerve was located at the point at which the mastoid process, the

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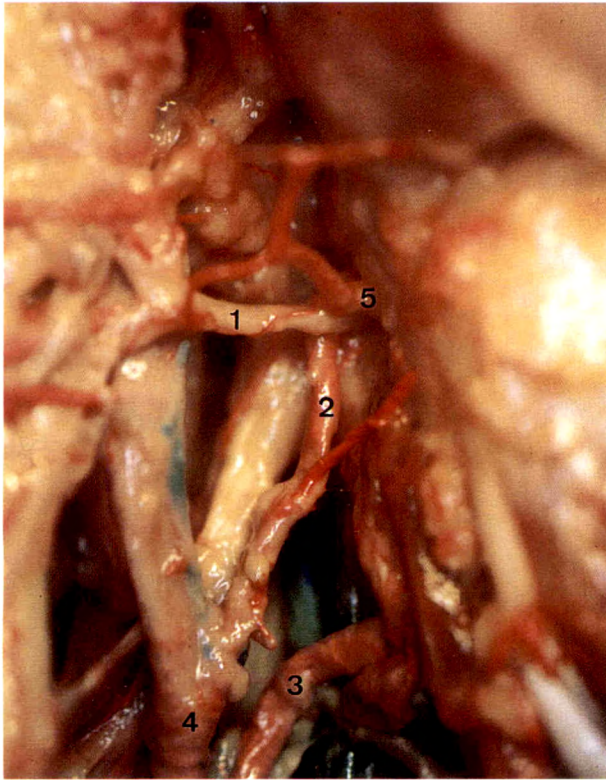


Fig 1. Intimate contact of trunk of left facial nerve with posterior auricular artery. 1 — trunk of facial nerve; 2 — posterior auricular artery; 3 — occipital artery; 4 — external carotid artery; 5 — stylomastoid artery.

cartilaginous portion of the auditory canal, and the superior border of the posterior belly of the digastric muscle meet. Once the main trunk of the facial nerve was identified, dissection proceeded in a plane superficial to the nerve toward the periphery of the gland and continued along the peripheral branches of the facial nerve. Each of its branches and all small arteries were meticulously dissected and entirely preserved.

RESULTS

In 21 cases (70%), the main trunk of the facial nerve had an intimate contact with the posterior auricular artery and its branches (Fig 1). The posterior auricular artery gave off 1 to 5 branches (mean, 3 branches), some of which supplied the parotid gland. Another of the branches, the stylomastoid artery, met the main trunk of the facial nerve before entering the stylomastoid foramen. In 6 cases (20%), the stylomastoid artery originated from the occipital artery (Fig 2). Its course was long (2.5 to 3.4 cm; mean, 2.7 cm) and posterior, and it always ran medially to the trunk of the facial nerve. In only 3 cases (10%), the stylomastoid artery arose directly from the external carotid artery (Fig 3). It always ran medially to the trunk of the facial nerve. There was no posterior auricular artery, and the external carotid artery gave off some voluminous branches to the parotid gland.

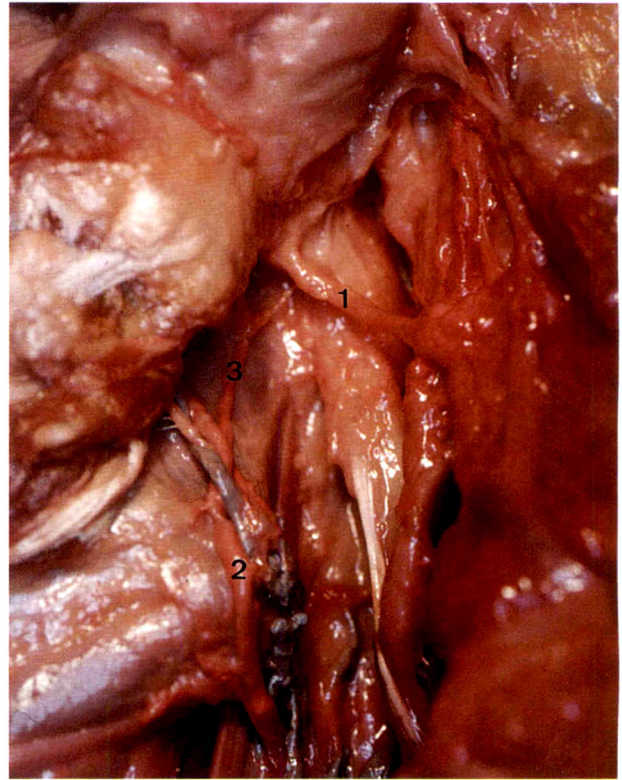


Fig 2. Right stylomastoid artery originating from occipital artery. 1 — trunk of facial nerve; 2 — occipital artery; 3 — stylomastoid artery.

In 19 of the 30 cases (63%), the stylomastoid artery passed medially to the trunk of the facial nerve. In the other 11 (37%), this artery passed laterally to the trunk of the facial nerve. In these cases, it always originated from the posterior auricular artery.

We considered the diameter of the stylomastoid artery "large" when it was greater than the diameter of the trunk of the facial nerve, which is 2 mm on average. Conversely, we considered it "small" when it was less than 2 mm. In 22 cases (73%), the diameter was small (0.5 to 2 mm; mean, 0.8 mm). In 8 cases (27%), the diameter was large (2.1 to 3 mm; mean, 2.3 mm). In these last 8 cases, the stylomastoid artery always originated from the posterior auricular artery and always passed laterally to the trunk of the facial nerve (see Table).

At its source, the distance from the stylomastoid artery to the trunk of the facial nerve was extremely variable (4 to 25 mm; mean, 11 mm), but this artery was always intimately related to the facial nerve at the level of the stylomastoid foramen. In this study, the arterial relationship to the facial nerve was bilaterally symmetric in each cadaver.

DISCUSSION

In the literature, the vascular-related anatomy of the trunk of the facial nerve is not described with

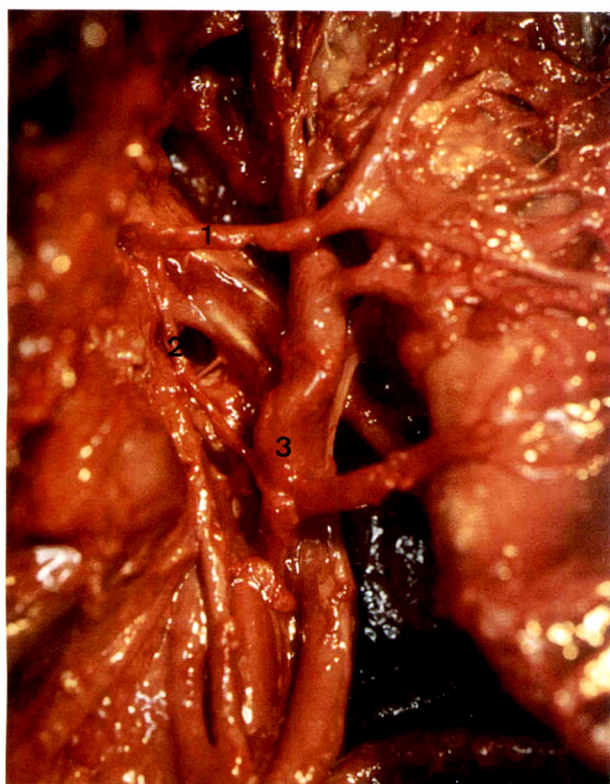


Fig 3. Right stylomastoid artery arising directly from carotid artery. 1 — trunk of facial nerve; 2 — stylomastoid artery; 3 — external carotid artery.

accuracy. In 1946, Dargent and Duroux⁴ stated that the auricular artery and its collateral branches were the only vessels in proximity to the nerve. They did not mention the stylomastoid artery. Then Beahrs and Adson² specified the course of all the branches of the external carotid artery that ran through the parotid space. They established that the occipital artery originates near the lower border of the digastric muscle. Although it passes close to the gland without making contact with it, this artery runs slightly upward and backward under cover of the digastric muscle. Just medial to the origin of this muscle, it grooves the mastoid process and runs posteriorly away from the parotid region. The posterior auricular artery arises near the upper border of the digastric muscle. It passes backward and upward along or superficial to this border to reach the interval between the mastoid process and the external auditory meatus. Beahrs and Adson stressed that its position on the anterior surface of the mastoid process is surgically significant, because it is usually encountered in the dissection used to expose the trunk of the facial nerve. They did not mention the stylomastoid artery. Most recent works on anatomy state that the stylomastoid artery most often originates from the posterior auricular artery.⁵⁻⁷ Conversely, Herdman et al,⁸ resuming the work of Djindjian and Merland,⁹ determined that this artery originated from the occipital artery in 60% of patients.

ORIGIN, RELATIONSHIP TO FACIAL NERVE, AND DIAMETER OF STYLOMASTOID ARTERY

	Origin			Relationship to Facial Nerve		Diameter	
	AP	Occ	Ext C	Medial	Lateral	Large (>2 mm)	Small (≤2 mm)
No. of cases	21	6	3	19	11	8	22
%	70	20	10	63	37	27	73

AP — auricular posterior artery, Occ — occipital artery, Ext C — external carotid artery.

Soudant¹⁰ also wrote that it originated from the occipital artery in two thirds of cases and rarely from the external carotid artery. In our study, we confirm that the stylomastoid artery originates mainly from the posterior auricular artery (70%), infrequently from the occipital artery (20%), and seldom from the external carotid artery (10%).

At the level of the stylomastoid foramen, most of the stylomastoid arteries (63%) entered on the medial aspect of the facial nerve. In only 11 of 30 cases (37%) did the stylomastoid artery pass on the lateral aspect of the facial nerve. In these 11 cases, the stylomastoid artery originated from the posterior auricular artery. Hemostasis of the stylomastoid artery will be dangerous for the facial nerve, because it passes laterally to it. Minatogawa et al³ described the intrinsic vascular anatomy of the facial nerve, but did not specify the origin of this artery. In their study, 20 of 30 stylomastoid arteries were medial, and 10 were anterior or lateral.

We studied the diameter of the stylomastoid artery. In the 8 cases (27%) in which this artery had a large caliber, it originated from the posterior auricular artery and passed lateral to the facial nerve at the stylomastoid foramen. In parotid surgery, these cases are especially dangerous, because the stylomastoid artery can mask the trunk of the facial nerve.

CONCLUSION

At the beginning of a parotidectomy, the main trunk of the facial nerve may be difficult to identify. The closest vascular relationship is to the stylomastoid artery. This artery originates from the posterior auricular artery in 70% of cases, from the occipital artery in 20% of cases, and directly from the external carotid artery in 10% of cases. It runs medially to the nerve in 63% of cases and laterally to the nerve in 37% of cases. Its diameter can be large — greater than 2 mm in 8 cases (27%). In these cases, the stylomastoid artery always runs laterally and in contact with the trunk of the facial nerve, masking it and making the surgical approach difficult during parotidectomy. Therefore, it is important to dissect this artery with caution.

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POSTOPERATIVE HEADACHE AFTER SURGERY FOR VESTIBULAR SCHWANNOMA

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Postoperative headache was studied among 251 patients who underwent operation for vestibular schwannoma. A questionnaire based on the McGill Pain Questionnaire and the Finnish Pain Questionnaire was sent to the patients. Twenty-one expressions describing postoperative headache were extracted with a factor analysis. The pain intensity was expressed on a visual analog scale, and the risk factors for postoperative headache were evaluated. Immediately after the operation, 154 subjects reported headache. Eighty-nine of the patients had had headache before operation, whereas 65 patients experienced headache only after operation. An average of 8.9 years after surgery, 93 patients still reported headache. Headache was a major problem for 27 subjects; 18 of the 27 had suffered from headache before operation. A retrosigmoidal approach, postoperative gait problems, preoperative headache, and small tumor size predicted postoperative problems with headache. When headache is present before operation, it tends to continue after operation, and if headache continues for 1 year, it usually persists without being reduced.

KEY WORDS — eighth cranial nerve tumors, pain questionnaire, risk factors for headache.

INTRODUCTION

Postoperative headache (POH) is a common consequence after vestibular schwannoma removal,¹ particularly when the operation is performed with the suboccipital or retrosigmoidal approach.²⁻⁴ When the surgical approach has been translabyrinthine, there is some disagreement about the occurrence of POH (Table 1^{1,2,5-14}).

The presence of headache even before operation has not often been mentioned in studies of POH after vestibular schwannoma surgery,^{2,3} although headache may be one of the symptoms of an extensive vestibular schwannoma itself. When preoperative headache has been mentioned, it has rarely been considered a cause of POH. The prevalence of preoperative headache varies from 9%⁸ to 48%.¹⁴

The cause of POH is open, but it is obvious that no single mechanism can be found.¹⁵ There is no specific treatment, but in general, its severity diminishes in due course.^{1,4}

The aim of the present work was to characterize the frequency, type, and magnitude of POH in a retrospective study of patients after vestibular schwannoma removal with special reference to possible risk factors and time course.

MATERIALS AND METHODS

All charts from 359 patients who underwent op-

TABLE 1. HEADACHE REPORTED IN LITERATURE AS OCCURRING BEFORE AND AFTER SURGERY FOR VESTIBULAR SCHWANNOMA

<i>Authors</i>	<i>Year</i>	<i>Preoperative Headache</i>	<i>Postoperative Headache</i>	<i>Type of Operative Approach</i>
Wiegand and Fickel ⁵	1989	36%	34%	
Schessel et al ²	1992		63.7% 0%	SO TL
Parving et al ⁶	1992		29%	TL
Harner et al ⁷	1995	Yes	17%/4% cranioplasty	RS
Pedrosa et al ⁸	1994	9%	73%/53%	SO, TL
Jorgensen and Pedersen ⁹	1994		27%/70%	TL, SO
Vijayan ¹	1995	42%	75%	
Kane et al ¹⁰	1995	33.9%	30.4%	SO
Ruckenstein et al ¹¹	1996		Yes	RS, TL
Catalano et al ¹²	1996	10%	51%	RS
Andersson et al ¹³	1997		22%	TL
Rigby et al ¹⁴	1997	48%	50%	TL, MF, RS

SO — suboccipital, TL — translabyrinthine, RS — retrosigmoidal, MF — middle fossa.

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TABLE 2. CHARACTERISTICS OF PATIENTS GROUPED BY SURGICAL APPROACH

Characteristics	RS	TL
Age (y)	47.1	52.9
Sex (M/F)	95/133	7/16
Follow-up time (y)	8.6	8.7
Severity of headache (No.)		
No headache	131	19
Mild	25	0
Moderate	47	2
Severe	25	2
Prevalence of preoperative headache (%)	49.6	39.1
Prevalence of postoperative headache (%)	42.5	17.3
Preoperative gait problems (%)	54.8	60.9
Preoperative hearing in tumor ear (1 kHz, dB)	52.2	73.3
Preoperative tinnitus (%)	63.6	56.5
Tumor diameter (mm)	21.5	18.2
Total (N)	228	23

RS — retrosigmoidal, TL — translabyrinthine.

eration for vestibular schwannoma at the Helsinki University Hospital between January 1979 and May 1993 were reviewed. Four patients with neurofibromatosis 2 were operated on bilaterally. The retrosigmoidal approach was used in 327 cases and the translabyrinthine approach in 36 cases. Thirty-seven of the 359 patients had died, and 5 could not be located. The patients had usually made follow-up visits 1 month and 1 year after operation.

A questionnaire based on the McGill Pain Questionnaire (MPQ)^{16,17} and the Finnish Pain Questionnaire^{18,19} was mailed to 317 patients, and 251 (79.2%) responded. Of the respondents, 149 were women (response rate, 81.0%) and 102 were men (response rate, 76.7%).

The MPQ is a tool for examining the dimensions of pain, and it provides quantitative information that can be assessed statistically.¹⁶ In the MPQ, pain is characterized by sensory, affective, and evaluative words.¹⁶ The questionnaire gives 54 pain words, synonyms in groups of 3 to 5, and from each group the patients are asked to choose the 1 word, when appropriate, that best characterizes their symptoms.

The intensity of POH was expressed on a visual analog scale (VAS) ranging from "no pain" (0) to "worst possible pain" (100).²⁰ The number of words chosen in the MPQ was also used to characterize pain intensity.¹⁶

The patients were asked to name factors provoking headache. Using a VAS, we grouped them into categories of "no or slight headache," "moderate headache," and "severe headache."

Preoperative headache can occur, for example, be-

TABLE 3. DISTRIBUTION OF HEADACHE OR NECK PAIN FELT ONE YEAR AFTER SURGERY

Area of Pain	POH	prePOH
Crown (%)	28.9	20.6
Ear (%)	0	7.9
Eye (%)	5.3	6.3
Face (%)	5.3	4.8
Forehead (%)	28.9	30.2
Neck (%)	71.1	68.3
Occiput (%)	76.3	71.4
Temple (%)	26.3	23.8
Total (N)	38/129	63/122

POH — patients with headaches only before operation; prePOH — patients with headaches both before and after operation.

cause of migraine, tension headache, increased intracranial brain pressure, compression of the trigeminal nerve, or other causes not related to the tumor. Therefore, the reason for headache before surgery in this patient group is difficult to classify. We defined the headache that commenced after surgery as POH. In the results we have classified the subjects with headache into 2 groups: the POH group and those who also had preoperative headache (prePOH group).

We analyzed the variables that characterized the patients' headaches by a factor analysis using simple correlation and varimax rotation. To find variables suggesting a risk of POH, we used a linear discriminant function analysis and logistic regression analysis. Duncan's multiple range test was used to compare the groups.

RESULTS

Altogether, 122 (48.6%) of the 251 patients who responded to our questionnaire had suffered from headache before surgery. Eighty-nine of the 122 patients suffered from headache 1 month after surgery (prePOH), and 65 patients who had not experienced headache before surgery suffered from headache 1 month after surgery (POH). The prevalence of POH was thus 50.4% after the surgery. The age of the subjects with POH varied from 16.4 to 64.8 years (mean, 46.7 years). The tumor was right-sided in 33 cases and left-sided in 32 cases. The largest diameter of the tumor varied from 3 to 40 mm (mean, 16.1 mm; Table 2). Sixty-three of 113 patients who had undergone the retrosigmoidal approach developed POH, as well as 2 of the 9 for whom the translabyrinthine approach had been used.

One hundred thirteen of the 122 patients in the prePOH group had undergone operation by the retrosigmoidal approach, and 9 patients had undergone the translabyrinthine procedure. In the prePOH group, age varied from 20.7 to 73.4 years (mean, 46.9 years). The tumor was right-sided in 56 cases and left-sided

TABLE 4. NUMBER OF WORDS CHOSEN IN MCGILL PAIN QUESTIONNAIRE ONE YEAR AFTER OPERATION

Degree of Pain	POH Group		prePOH Group	
	No. of Patients	Mean No. of Words Chosen	No. of Patients	Mean No. of Words Chosen
Slight	9	6.7	17	6.8
Moderate	17	7.4	27	7.6
Severe	12	8.8	19	7.4
Total	38	7.6	63	7.2

in 66 cases. The largest diameter of the tumor varied from 5 to 65 mm, with a mean of 23.7 mm (Table 2).

The patients with POH experienced their headache mainly in the area of the neck (71%) and the occiput (76%), regardless of the surgical approach. There was no pain around the ear. Also, in the prePOH group, the headache was experienced mainly around the occiput (71%) and the neck (69%) after the operation (Table 3). In both groups, the pain was typically unilateral and felt on the side of the surgery.

The mean number of words chosen on the MPQ was 7.6 (SD, 4) in the POH group and 7.2 (SD, 4) in the prePOH group. The mean number of words chosen was also calculated for the severity of the headaches. The data are presented in Table 4.

Emotional stress, physical stress, bending down, and being awake were the main headache-provoking factors after surgery in both groups. Physical stress became the most provocative factor when the headache continued (Table 5).

The patients with POH described their headache with 4 sensory words (intermittent, 1-sided, lacerating, sore) and 1 evaluative word (troublesome). In the prePOH group, the headache after the operation was described, in most cases, with 5 sensory words (1-sided, intermittent, hot, lacerating, sore) and 3 evaluative words (troublesome, intense, painful). From the MPQ, 54 words were selected for a correlation matrix. If 2 words had a strong correlation ($r \geq$

TABLE 5. FACTORS THAT PROVOKED HEADACHES 1 MONTH AND 8.9 YEARS AFTER OPERATION

Provoking Factor	POH Group		PrePOH Group	
	1 mo (N = 65)	8.9 y (N = 35)	1 mo (N = 89)	8.9 y (N = 58)
Being awake	23.1	31.4	28.1	34.5
Bending down	26.2	28.6	36	44.8
Certain food	0	0	2.2	1.7
Cigarette smoke	7.7	20	15.7	22.4
Menstruation	4.6	5.7	5.6	10.3
Physical stress	23.1	62.9	40.4	60.3
Emotional stress	27.7	45.7	24.7	43.1

Data are percentages.

.5, $p = .001$) in the correlation matrix, only 1 was selected for factor analysis. According to the correlation matrix, the following 21 words described POH well: billowy, oppressive, sore, irritating, freezing, continuous, beating, smarting, intense, hot, cold, lacerating, crushing, superficial, burning, unbearable, deep, 1-sided, annoying, sickening, and wrenching. These words were selected for a factor analysis, which produced 6 factors. The first factor was named "sore," and it accounted for 24.3% of variance in pain, the main words being the sensory words "sore" and "lacerating" and the affective word "annoying." The sore factor described the combined components of pain. The second factor, "billowy," consisting mainly of sensory and sensory-thermal properties of pain, accounted for 14.9% of the variance, the words "billowy" and "hot" having the highest scores. The third factor, "smarting," accounted for 9.5% of the variance and consisted mainly of the sensory words "smarting" and "cold" and the affective word "sickening." The fourth factor, "irritating," consisted mainly of the affective word "irritating" and accounted for 8.5% of the variance. The other factors accounted for 7.4% and 6.6% of the variance and were named "deep" and "oppressive," respectively. These 6 factors accounted for 71.2% of the variance in POH.

Headache was also studied in the same manner in the prePOH group. This time, a correlation matrix with the same criteria gave 8 words that described headache. They were oppressive, freezing, frightful, terrifying, sickening, superficial, lacerating, and wrenching. A factor analysis gave 4 factors that accounted for 69.3% of the variance in pain: the first factor, "sickening," accounted for 21.4% of the variance; the second, "wrenching," accounted for 19.0% of the variance; the third, "frightful," accounted for 15.3% of the variance; and the fourth, "terrifying," accounted for 13.6% of the variance. Pain had some influence on everyday life for 55 patients, 27 having moderate or considerable difficulties. Twenty of these 55 patients suffered from headache only after surgery; the others had also had headache before surgery.

One month after the operation, the prevalence of POH was 50.4%; 1 year after the operation, it had dropped to 29.5%; and at the time of the questionnaire, at a mean of 8.9 years after surgery, the prevalence was 27.1%. In the prePOH group, the prevalence of POH was 73% at 1 month after the operation. One year after the operation, it was 51.6%, and 8.9 years after the operation, it was 47.5% (Fig 1).

The maximum pain intensity of the headache at 1 year after the surgery varied from 5 to 100 (mean, 18.6; SD, 32.8), and the pain minimum ranged from

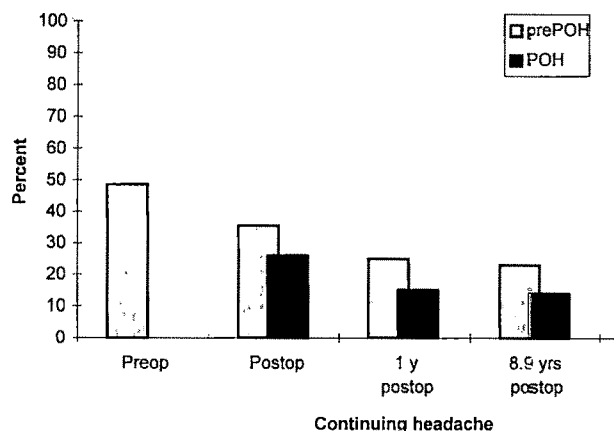


Fig 1. Continuing headache among patients with headache before operation (prePOH) and among patients with no headache before operation (POH). Total number of patients is 251.

5 to 71 (mean, 3.7; SD, 10.6) in the POH group. At 8.9 years, the mean of the maximum pain ratings was 11.8.

In the prePOH group, the mean maximum and minimum pain intensities were 33.3 (SD, 37.0) and 6.1 (SD, 11.9), respectively. At 8.9 years, the mean of the maximum rating was 29.1.

The severity of the POH declined more among the POH patients than among the prePOH patients (χ^2 , $p > .05$; Fig 2). Of the 35 patients with POH 8.9 years after surgery, 26% did not need pain medication, 29% found symptomatic treatment and anti-inflammatory agents very helpful, and the rest (46%) had at least some benefit from anti-inflammatory agents. Of the 58 patients in the prePOH group, 52% considered symptomatic treatment and anti-inflammatory agents very helpful, 28% had received some benefit from them, 17% did not need any medication, and 3% received no help from medication.

The following variables were included in the step-

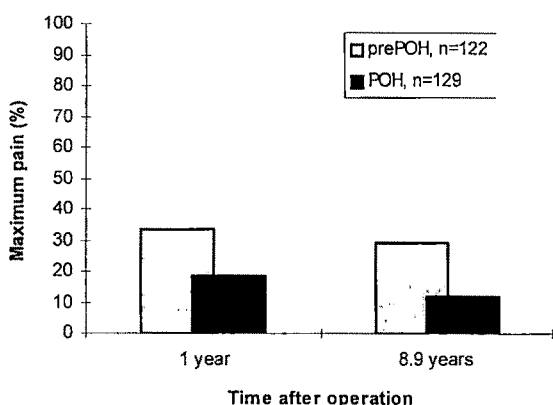


Fig 2. Maximum pain 1 year after operation and 8.9 years after operation for patients with headache before operation (prePOH) and those with no headache before operation (POH).

TABLE 6. VARIABLES SIGNIFICANT IN ASSOCIATION WITH POSTOPERATIVE HEADACHE ACCORDING TO LOGISTIC REGRESSION ANALYSIS

Variable	B	SE	Wald	df	Sig	R	Exp(B)
Postoperative gait disorders	0.895	.292	9.370	1	.002	.148	2.448
Surgical approach	1.334	.593	5.058	1	.026	.096	3.799
Tumor size	-0.045	.012	12.667	1	.0004	-.179	0.955
Pain before operation	0.923	.291	10.023	1	.002	.154	2.518

B — estimated coefficient, Wald — Wald statistic, Sig — significance level, Exp(B) — increase of odds.

wise logistic regression analysis in the search for factors associated with POH: headache before the operation, tumor size, age, severity of tinnitus, surgical approach, hearing of the affected ear, preoperative caloric responses, and postoperative gait disturbance. The model consisting of preoperative headache, surgical approach, postoperative gait disorders, and tumor size was statistically highly significant ($p < .001$) when analyzed with the maximum likelihood method. It predicted POH for 68.1% of the patients. The surgical approach ($p < .05$) was the most important single risk factor linked to severe postoperative headache, the odds ratio (OR) being 3.9 with the retrosigmoidal approach (Table 6). Preoperative headache was a statistically significant risk factor ($p < .05$) for POH (OR, 2.5), and postoperative gait disorders increased the risk for POH (OR, 2.4; $p < .05$). A small tumor size was also a risk factor (OR, 1.1; $p < .01$).

When we considered only the patients with POH, the logistic regression analysis showed that the retrosigmoidal surgical approach increased the risk for POH (OR, 5.8; $p < .05$).

Although women dominated the headache group (149 women and 102 men answered the questionnaire), gender was not important with respect to the severity of the headaches.

DISCUSSION

The exact cause of preoperative headache could not be determined, because only the elements of the POH were subjected to analysis in this study. Some of the preoperative headaches are probably unrelated to the tumor surgery and, as expected, persist once the tumor is removed. Thus, the data set does not exclude non-tumor-related and non-surgery-related headache patterns such as migraine, which would be expected to persist after surgery. The role of migrainous headache remains open as a causative factor. The tumor diameter was more than 30 mm in 24.6% of the patients with preoperative headache, and the headache vanished in 50% of them after operation. We separated the headaches into preopera-

tive headache and only POH in order to study the headache that appeared first after operation. The POH is studied in detail elsewhere (Levo et al, unpublished observations) and is linked to trigeminal irritation caused by bone dust irritation or manipulation of the sensitive dura-periosteal complex.

The POH was experienced in the neck and occiput areas among the patients who underwent the retrosigmoidal or translabyrinthine approach. The pain was unilateral and on the side of the operation, as shown in other studies.¹ The pain mimicked cervicogenic headache pain, which is also unilateral and originates in the neck and then spreads to the head.²¹ Thus, the location of pain did not provide any hints as to the cause of POH.^{15,22}

The POH following vestibular schwannoma surgery varies in character. Patients choose different sensory words to describe their headache. "Intermittent," "one-sided," "lacerating," and "sore" were the most commonly used words. Chronic pain brought affective attributes to the descriptions^{19,23} of the POH patients, with the words "frightful," "sickening," and "irritating." The evaluative word used most was "annoying."

Acute pain involves less differentiation of sensory, affective, and evaluative language dimensions.²³ The patients with prePOH used more affective words to describe the headache than did the patients with POH. The result indicates that the prePOH headaches were more severe and more prolonged. Thus, POH differs from chronic pain and seems to be more acute in nature. This conclusion implies that the pain of the POH group was not continuous, but was intermittent in nature instead, contrasting with the pain of the prePOH group. The patients with prePOH also used more evaluative words in describing their POHs than did patients with only POH, a finding that indicates greater severity for their headaches.

The factor analysis gave 6 factors consisting of 21 different words that accounted for 71.2% of the variance of the pain in the POH group. All these factors characterized the POH by sensory words; only the factor "sore" contained an affective component; and the factor "oppressive" was mainly affective by nature. In the prePOH group, the factor analysis consisted of only 8 different words and gave 4 factors, which accounted for 69.3% of the variance in headache. The headache in the prePOH group was more affective; the factor "sickening" and the factor "terrifying" were mainly affective; and the factor "frightful" was both sensory and affective. Only 1 factor, "wrenching," was sensory in nature. This result fits well the assumption mentioned earlier that acute pain involves less differentiation of dimensions of pain

than does chronic pain, which also elicits afferent language dimensions.

The number of words chosen was higher in the POH group than in the prePOH group, even when both groups were divided into subgroups according to the degree of headache. Therefore, chronic pain does not elicit more verbal description than acute pain does.

The mean intensity of maximum pain was lower for the patients with POH than for those with prePOH. When compared with the results of the MPQ difficulties in everyday life, the problems did not seem as prominent, however. When the pain intensity varied from "no pain" to "worst possible pain," only 27 patients (10.7%) reported having considerable difficulties in everyday life because of headaches. Two of them had undergone a translabyrinthine approach, and for the rest, the retrosigmoidal approach had been used. Most of the patients did not have difficulties in coping with POH.

In agreement with other authors,¹ we observed that headache after an operation for vestibular schwannoma declines during the first year. Almost 60% had headache immediately after the operation, and a significant number of these persons had had headaches before surgery. One year after surgery, the proportion with POH was 40%, and headaches were more common among the patients with prePOH. The headaches continued to decrease, being 27% for the POH group and 48% for the prePOH group approximately 8.9 years after the surgery. Our results indicate that if headache persists for 1 year, it will remain persistent, and no significant reduction in the maximum pain intensity can be expected.

Symptomatic treatment and common anti-inflammatory agents were considered helpful, and the majority in both patient groups received at least some benefit from them. The patients with prePOH also suffered from more severe headache than did the patients with POH. The only 3 persons who did not benefit from anti-inflammatory agents at all were prePOH patients.

According to logistic regression analysis, the retrosigmoidal approach increased the risk for POH by 3.8 times, and it was the single most important risk factor. Severe postoperative gait disorder also increased the risk for POH, as did preoperative headache and a small tumor size. Postoperative gait disorders may be linked to vestibular imbalance, and vestibular imbalance may provoke an increase in neck muscle tone that leads to symptoms mimicking "tension neck syndrome." A small tumor size has earlier been observed to trigger POH.

For patients with a deaf ear and a small tumor and

with preoperative headache, it is advisable to operate by the translabyrinthine approach. The patients should be warned about POH if the risk factors are present.

It may be problematic to call a headache POH when the patient has had preoperative headaches and there is no confirmed cause for the POH. Hitherto, most reports called all reported headache POH, even though the headache may not have been a result of the surgery. The prevalence of prePOH is not reported in most studies.² However, for 3, it varied from 9%⁸ to 36%⁵ to 42%.¹ The questioning technique and the classification of troublesome headache may explain the difference between these studies and our study. We classified all headaches reported before surgery as prePOH, without screening out occasional or slight headaches.

Postoperative headache is usually connected with the suboccipital or retrosigmoidal approach in surgery for vestibular schwannoma,² and up to 73% of patients who have POH have undergone the suboccipital approach.⁸ Postoperative headache was reported after vestibular schwannoma surgery through

the middle fossa approach for 34% of 541 patients.⁵ The incidence of POH after the translabyrinthine approach has varied from 0%² to 75%.¹ In our study, the incidence of POH after the translabyrinthine approach was 39%. Thus, none of the operative approaches are without risk for POH, but in our study the retrosigmoidal approach carried a 3.8 times higher risk than the translabyrinthine procedure.

CONCLUSION

Postoperative headache can be a severe problem after vestibular schwannoma surgery. We found that if headache is present before the operation, it tends to continue afterward. In our study, 122 (48.6%) patients gave a history of preoperative headache, and of these, 89 gave a history of POH. In addition, POH developed in 65 (23.9%) patients without preoperative headache. If POH continues for 1 year, it usually persists without its severity's being reduced.

Risk factors for POH, according to our findings, were the retrosigmoidal approach, severe postoperative gait disorders, preoperative headache, and a small tumor size.

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ARTIFACTUAL THICKENING OF THE SINUS WALLS ON COMPUTED TOMOGRAPHY: A PHANTOM MODEL AND CLINICAL STUDY

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Measuring sinus wall thickness on computed tomography may be important for distinguishing between acute and chronic inflammation of the paranasal sinuses or in cases of a suspected neoplasm. The objective of this study was to investigate the effects of opacified and aerated sinuses on the appearance of sinus wall thickness. A phantom model consisting of a skull half-immersed in water was scanned, and various slice thicknesses and different windows were used. The sinus walls of the water-immersed side appeared to be thicker than those of the aerated side. Bone windows did not completely eliminate this partial volume effect. It was concluded that comparison between a fluid- or tissue-filled sinus and an air-filled counterpart is not accurate enough for evaluating sinus wall thickness. Bone windows do not completely eliminate the artifactual thickening of the bony wall of a filled sinus.

KEY WORDS — computed tomography, paranasal sinuses, partial volume effect, sinus wall thickness.

INTRODUCTION

Computed tomography (CT) has replaced plain x-ray films as the imaging method of choice for the diagnosis and evaluation of sinus infections or tumoral diseases. It enables an examination of the cavity as well as the bony walls of the sinuses. The diagnosis of chronic sinusitis is primarily based on clinical history and physical examination. A CT examination may be helpful in confirming the diagnosis. Bone sclerosis with bone thickening is considered to be a sign of chronic infection,¹⁻⁴ whereas resorption or disappearance of the bony wall may be a sign of a benign or malignant tumor. The so-called "partial volume effect" (PVE) may give rise to errors in the assessment of sinus wall thickness. A bone-fluid interface, as in cases with pus or a tumor within the sinus cavity, contributes to the PVE. In such cases, assessment of sinus wall thickness might be inaccurate if a unilaterally fluid-filled sinus is compared with the air-filled cavity on the other side. Bone windows and high-resolution thin sections are helpful in minimizing the effect of the PVE. We investigated the PVE phenomenon and the effects of different acquisition parameters on the apparent wall thickness in sinuses filled with fluids.

For a better understanding of this phenomenon, a review of the basic principles of CT scan formation is necessary. Each CT slice is composed of a grid of small blocks called "volume elements" or voxels. A number assigned to each voxel reflects the average attenuation value of the tissue within it and is there-

fore related to the amount of absorbed radiation. The attenuation value is measured in Hounsfield units (HU) ranging in scale from -1,000 for air to +1,000 or above for dense structures such as cortical bone. Water has a value of 0, and most soft tissues range from -200 to +200 HU. Large numbers are represented by light shades of gray, and small numbers by dark shades of gray. To present this information, different CT windows have been developed. As soft tissue windows have values around -200 HU to +200 HU, voxels with attenuation values exceeding +200 HU "appear" white, and those below -200 "appear" black. Bone windows have values ranging from +100 to +800 HU or above. Thus, voxels with attenuation values of less than +100 HU appear black and are indistinguishable from air. The PVE affects image production when 2 structures with different HU values coexist within the same voxel (eg, bone and fluid). Under these circumstances, an average of the 2 attenuation values is generated. The visibility of the PVE also depends on the viewing window and on the size of the acquisition voxel.

Figure 1 shows how the adjacent tissue may modify the "appearance" of sinus wall thickness because of the PVE. In the upper part of the Figure, a bony wall with +800 HU and an overlay of the image voxels is presented. In the highlighted voxel, bone occupies 25% of the volume, whereas the adjacent tissue occupies the remaining 75%. If the bone is surrounded by air, the average attenuation value in the highlighted voxel is -550 HU $[(-1,000 \times 0.75) + (+800 \times 0.25)]$,

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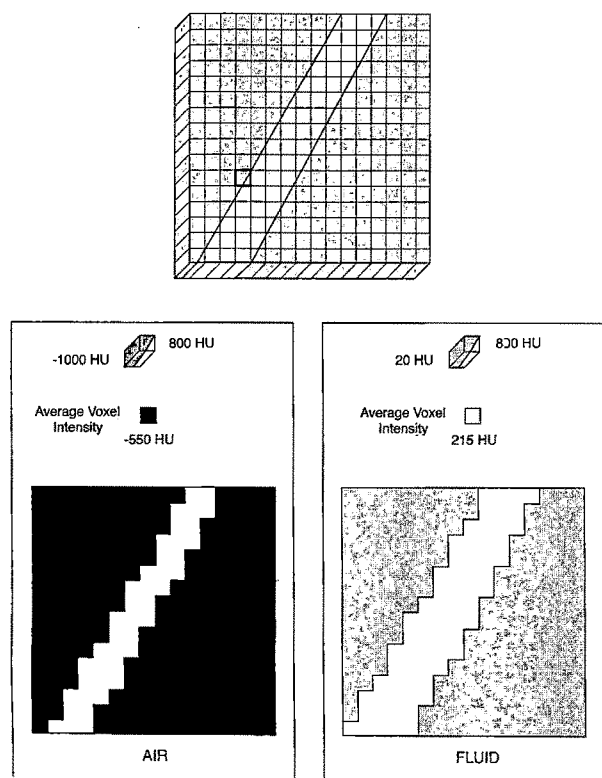


Fig 1. Effect of partial volume summation of bone-fluid or bone-air interface on resultant voxel intensities and apparent thickness of bony wall. At top is computed tomography (CT) model of bony wall with overlay of image voxels. Highlighted voxel partially includes bony wall and air or fluid contents of sinus. At bottom left, bony wall (+800 Hounsfield units [HU]) is placed in air (-1,000 HU). In outlined voxel, in which bone represents 25% of volume, average attenuation value is around -550 HU $[(-1,000 \times 0.75) + (+800 \times 0.25)]$, and thus voxel appears to be black (like air) in soft tissue windows of -200 to +200 HU. At bottom right, in same soft tissue window, if bony wall is placed in fluid (+20 HU), average attenuation value in same voxel is +215 HU $[(+20 \times 0.75) + (+800 \times 0.25)]$, and it appears to be white, like bone. Therefore, with same CT parameters, bony wall will "appear" to be thicker in fluid than in air.

and it appears to be black, like air. If the bony wall is placed in a fluid environment of +20 HU, the average attenuation value in the same voxel is +215 HU $[(+20 \times 0.75) + (+800 \times 0.25)]$, and it appears to be white, like bone. Therefore, with the same scanning parameters, the bony wall can appear to be thicker in fluid than in air. A larger voxel, which results from a thicker slice, exacerbates this phenomenon.

This study examines the effect of an opacified (fluid-filled) and an empty (air-filled) sinus on the "appearance" of sinus wall thickness. Images of a phantom model were obtained with different slice thicknesses and were viewed by means of different windows. Two clinical cases of patients with unilateral sinus disorders are presented to illustrate the PVE phenomenon.

MATERIALS AND METHODS

Phantom Model. A skull was positioned on its side and was half-immersed in water so that the fluid level reached the midsagittal plane. One side of the paranasal sinuses was therefore fully immersed in water, while the other remained aerated. The skull was scanned at different levels by an Elscint CT Elite 2400 (Haifa, Israel) with 1.2-mm-, 2.5-mm-, and 5-mm-thick slices. For the 1.2-mm slice, the acquisition matrix was 512×512 , with a field of view (FOV) of 240 mm, ie, 0.5×0.5 mm pixel size. For the 2.5-mm and 5-mm slices, the acquisition matrix was 340×340 , with the same FOV of 240 mm, ie, 0.7×0.7 mm pixel size. Scanning was performed with 140 kilovolts (peak), 315 milliamperes second, and 2.1-second tube rotation. Each slice was viewed by means of a soft tissue window (-112 to +250 HU) and a bone window (-350 to +1,015 HU).

Clinical Examples. Patient 1 was a 7-year-old boy with left acute ethmoiditis. A contrast CT scan was performed with soft tissue windows (-32 to +130 HU) and bone windows (-754 to +1,586 HU). In both image presentations, 2.5-mm-thick slices, a 340×340 reconstruction matrix, and a FOV of 240 mm were used.

Patient 2 was a 27-year-old woman with right maxillary sinusitis. Soft tissue windows (-207 to +219 HU, 5-mm-thick slices, a reconstruction matrix of 340×340 , and an FOV of 240 mm), as well as bone windows (-982 to +2,372 HU, 1-mm-thick slices, a reconstruction matrix of 512×512 , and an FOV of 240 mm) were used.

RESULTS

The "appearance" of the sinus walls of the phantom model confirmed the theoretical hypothesis. In Fig 2, 6 different slices at the level of the maxillary sinus are presented. In the upper part, bone windows of 1.2-mm (Fig 2A), 2.5-mm (Fig 2B), and 5-mm (Fig 2C) thickness are shown, and at the bottom, soft tissue windows of the same respective thicknesses are shown (Fig 2D-F). On the aerated side, as the slice becomes thicker, the maxillary sinus wall appears to be thinner as a result of the PVE; on the fluid-filled side, as the slice becomes thicker, the sinus wall appears to be thicker. This effect is less obvious on bone windows, but it still exists. The same observations were made at the levels of the ethmoid and the frontal sinuses.

In patient 1, an axial CT scan with contrast material was performed to rule out a periorbital abscess. In soft tissue windows (Fig 3A), the walls and septa of the left ethmoid sinus appear to be thicker than

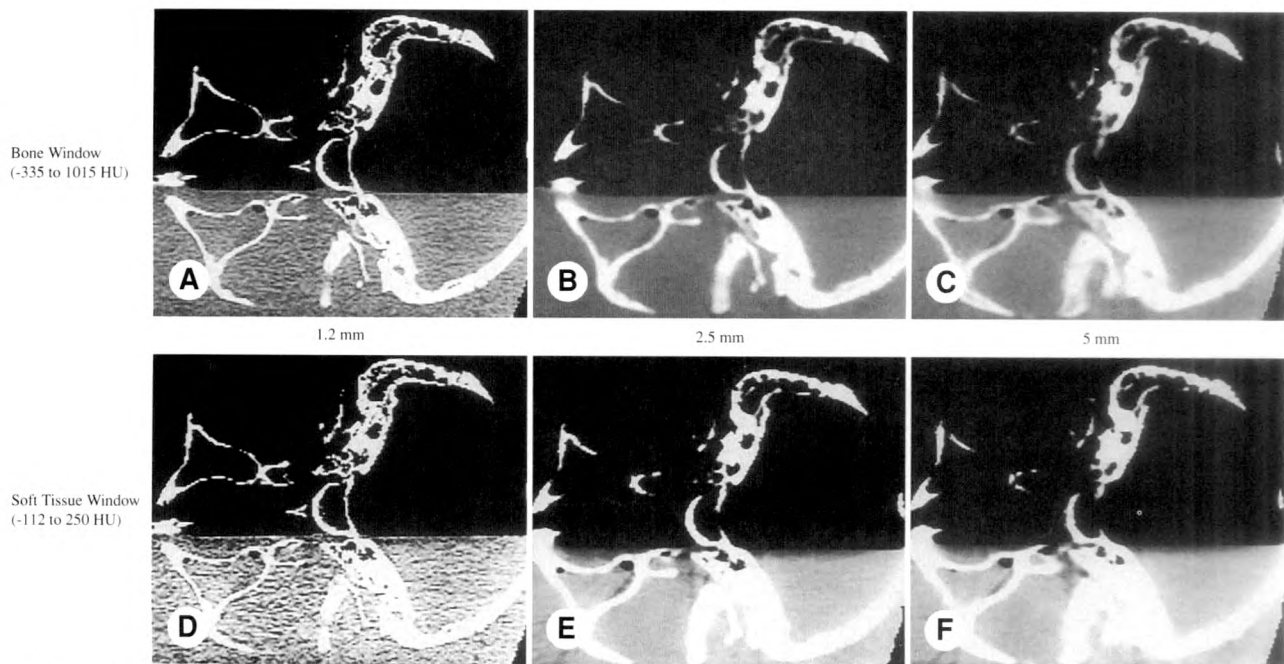


Fig 2. Phantom model (skull positioned on its side, half-immersed in water) was scanned with bone window (-335 to $+1,015$ HU) with thicknesses of 1.2 mm (A), 2.5 mm (B), and 5 mm (C) and with soft tissue window (-112 to $+250$ HU) with thicknesses of 1.2 mm (D), 2.5 mm (E), and 5 mm (F). On aerated side, as slice becomes thicker, maxillary sinus wall appears to be thinner because of partial volume effect (PVE); on fluid-filled side, as slice becomes thicker, sinus wall appears to be thicker, because of PVE with air or fluid, respectively. This effect is amplified when soft tissue windows are used (D-F).

those of the right side, where they partially disappear. In bone windows (Fig 3B), the sinus walls are similar, although the septa are identified with difficulty on the right.

In the CT scan of patient 2, with soft tissue windows (Fig 4A), the walls of the right maxillary sinus appear to be artifactually thick because of the PVE with pus in the sinus. In the very thin (1 mm) bone window section (Fig 4B), the thicknesses of both

sides appear to be similar. Such thin sections are not used routinely in CT scanning of the sinuses, but in this case it was done to study the thickness of the maxillary bony wall more precisely.

DISCUSSION

It is well known that bone windows are suitable for CT imaging of the paranasal sinuses, but the effect of the adjacent tissue on the "appearance" of



Fig 3. (Patient 1) Axial CT scan of 7-year-old boy with left acute ethmoiditis with soft tissue bulging over nasal bridge. A) Bone window, -754 to $+1,586$ HU. B) Soft tissue window, -32 to $+130$ HU (with contrast). In soft tissue windows, walls and septa of left ethmoid sinus appear to be thicker than on right side, where they are partially eliminated. In bone windows, sinus walls are similar, although septa are identified with difficulty on right.

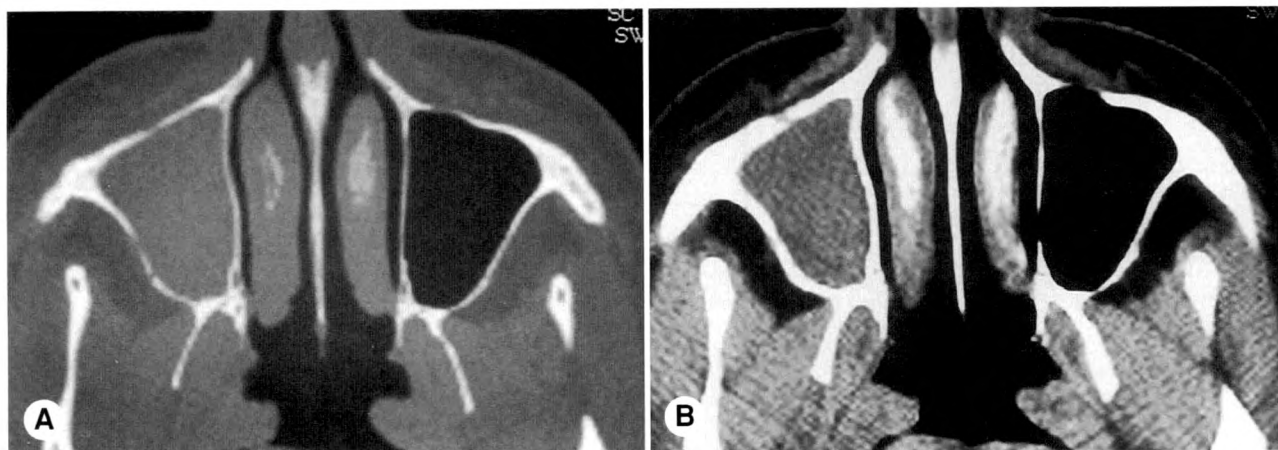


Fig 4. (Patient 2) Axial CT scan of 27-year-old woman with right maxillary sinusitis. A) Bone window, -982 to $+2,372$ HU, 1-mm slice thickness. B) Soft tissue window, -207 to $+219$ HU, 5-mm slice thickness. With soft tissue windows (B), walls of right maxillary sinus appear to be artifactually thick because of PVE with pus in sinus. On bone window imaging (A), thicknesses of both sides appear to be fairly similar.

bone has evidently received little attention to this point. The phenomenon of the PVE is well described in the literature in relation to lung nodules,⁵ but to the best of our knowledge, ours is the first study on the paranasal sinuses. It demonstrates that any comparison between an air-filled sinus and its fluid- or tissue-filled counterpart does not accurately reflect bony wall thickness.

Artifactual thickening of the bony walls of a filled sinus is essentially seen in soft tissue windows; it is also seen in bone windows, but less apparently. In cases in which tumoral disease or an extended infection outside the sinus cavity is suspected, soft tissue windows are the technique of choice. A clinician may be interested in comparing a pathological filled sinus with its contralateral empty sinus, in which case

bone windows are preferred.

It should be emphasized that in the semi-immersed skull model, the PVE was amplified on the aerated side because of the absence of soft tissue structures such as fat and muscle, which are normally located outside the sinus. However, the 2 clinical cases clearly demonstrated a discrepancy between the apparent thicknesses of the sinus wall on both sides, and they support the experimental observations.

In conclusion, the sinus wall thickness of a filled sinus should not be compared with that of its empty counterpart. The PVE may cause overestimation of the wall thickness of a filled sinus, or underestimation of bone erosion in cases involving a tumor. Bone windows do not completely eliminate this phenomenon, especially when thick slices are used.

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MANAGEMENT OF LARGE MOHS DEFECTS

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This study was performed to determine the appropriateness and relative merits of closing Mohs defects of the head and neck at the time of surgery or after surgery, in contrast with allowing defects to heal spontaneously. For 185 patients who had large Mohs wounds of the head and neck (scalp, nose, cheek, forehead, lip, chin, ear, or neck) that healed spontaneously and who underwent postoperative reconstruction as required, we recorded wound location, size, and depth. We then evaluated the cosmesis and functional result periodically and ≥ 6 months after operation by chart review, interview, or both. We found that large wounds of the scalp, neck, and ear (except through-and-through defects) often heal spontaneously with acceptable cosmesis. Large defects of the nose usually require prompt reconstruction. Large defects of the central cheek, lip, and chin usually heal spontaneously with poor cosmesis. However, we often reserve surgery for an unacceptable cosmetic result, because repairing a small scar is often less complex than reconstructing a large Mohs defect. We conclude that spontaneous healing of selected Mohs wounds of the head and neck can result in satisfactory cosmesis and function, thus obviating or minimizing the need for complex surgical repair. Surgeons can select management of Mohs wounds effectively and efficiently by accurately predicting the final cosmetic and functional result of spontaneous healing, thus reserving surgery for unfavorable cosmetic or functional results.

KEY WORDS — facial wounds, Mohs, Mohs surgery.

INTRODUCTION

Skin defects of the head and neck may be reconstructed at surgery, delayed for a time, or allowed to heal by secondary intention. Most surgeons prefer prompt reconstruction, because they believe that wound closure shortens healing time, avoids pain and infection, and enhances cosmesis. However, allowing wounds to heal by secondary intention, although often prolonged, offers the advantages of optimal cancer surveillance, simplified wound care, avoidance of reconstructive procedures and the associated costs and potential complications, and, in selected cases, comparable or even superior cosmetic results.

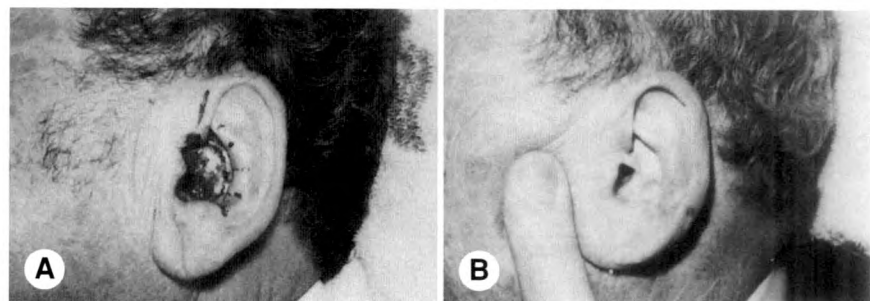
Whereas small wounds of the head and neck are often closed primarily, large defects may require complex and lengthy reconstructive procedures. An alternative treatment option is to allow selected

wounds to heal by secondary intention and to reserve surgery for repair of unfavorable results. However, the course of wound healing and the final cosmetic result must be accurately predicted when selecting patients for surgical repair or healing by secondary intention. This study evaluated our experience in managing large defects of the head and neck in order to compare the benefits of these treatment options.¹⁻⁴

PATIENTS AND METHODS

We included in the study members of the Kaiser Foundation Health Plan who were referred by physicians of the Southern California Permanente Medical Group to the Mohs Surgery Center, a regional referral center at our Panorama City Medical Center, where 600 to 800 new patients each year are seen and treated surgically by one of the authors (L.A.A.).

Fig 1. A) Intraoperative photograph shows skin of entire concha removed, exposing cartilage. B) Photograph taken 10 years after operation shows excellent result in which ear appears normal and has no canal stenosis. Defect epithelialized in 8 weeks.



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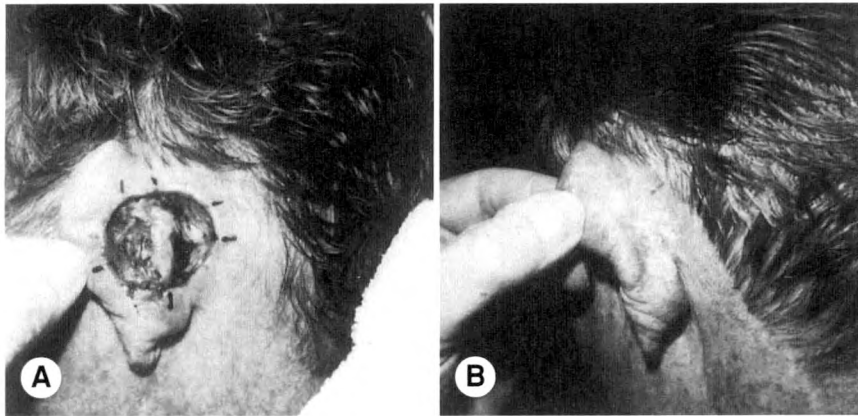


Fig 2. A) Intraoperative photograph shows defect of posterior aspect of ear, sulcus, and mastoid skin with centrally exposed cartilage. B) Photograph taken 6 years after operation shows excellent result with minimal webbing. Wound healed in 6 weeks.

More than 8,000 patients have been treated at the center, where local anesthesia and the fresh tissue technique are used exclusively.

On an unselected basis, we interviewed or reviewed the charts of patients who had large defects of the head and neck resulting from Mohs surgery during the past 14 years. Variables recorded included age and sex of patients; wound location, size, and depth; scar size; time required for the wound to epithelialize; whether the tumor was primary or recurrent; and the type of previous therapy received. The greatest length, width, and depth of the wound were measured with a millimeter rule and caliper. The depth of the wound was also described by anatomic layer exposed.

Wound care was designed to keep the wound moist and to promote a granulating base. Patients were instructed to cleanse the wound with 3% hydrogen peroxide daily, then to apply polymyxin B–bacitracin ointment and a dressing. Bathing or showering over the exposed wound was allowed. No prophylactic antibiotics or analgesics (except acetaminophen) were routinely used.

Photographs were taken before and immediately

after surgery, and patients were evaluated weekly until the wound epithelialized. Wounds were then photographed and evaluated at increasingly longer intervals. By consensus of the authors, the final cosmetic result was documented as poor, good, or excellent after ≥ 6 months of follow-up. A scar that was unsightly or that attracted attention was considered a poor result. An excellent result was defined as a wound that was imperceptible unless brought to the attention of the examiner. A good result was defined as a wound that was noticeable but that blended with the lines or contour of the face or neck so as not to attract attention.

For documentation, the head and neck were divided into the following units (listed with number of patients who had wounds in the respective unit): scalp (35 patients), forehead (40), nose (17), cheek (32), ear (21), lip (19), chin (7), and neck (14). A large defect was arbitrarily defined as encompassing $>30\%$ of the surface area of the affected unit or having a diameter of 3 to 10 cm; a very large wound was defined as >10 cm. The majority of Mohs wounds are circular or ovoid, and the surface area is easily calculated. Note that a 1- or 2-cm defect may be considered large in some units (eg, nose and ear) but small

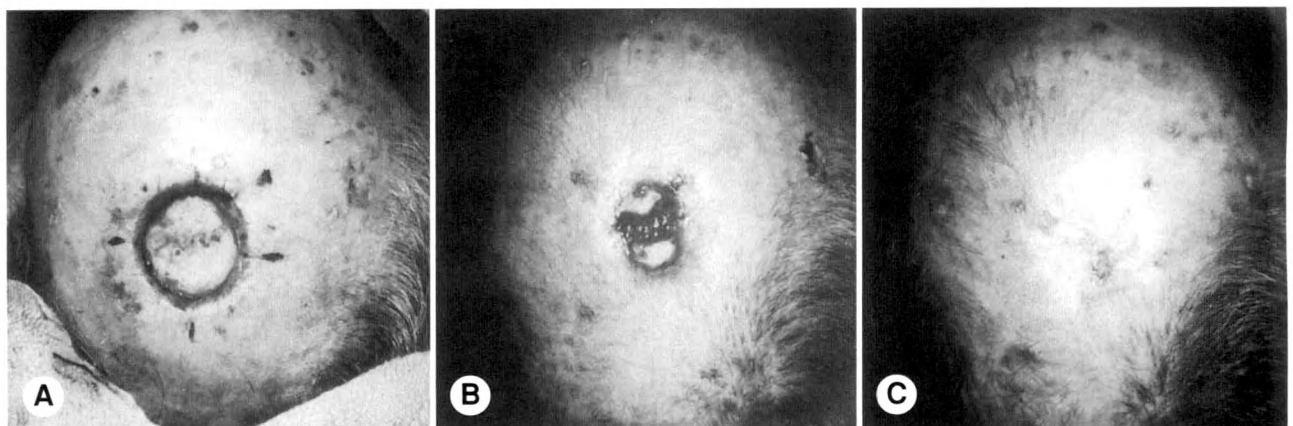
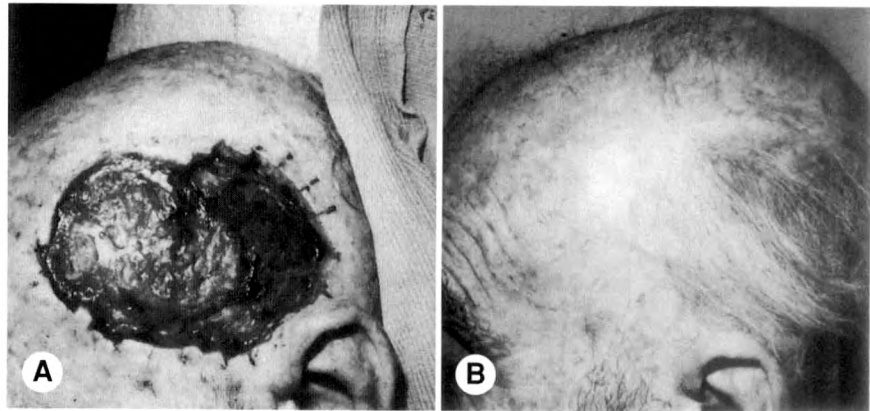


Fig 3. A) Intraoperative photograph shows 4-cm scalp wound and exposed bone denuded of periosteum. B) Photograph taken 2 weeks after operation shows wound greatly contracted and granulating well. C) Photograph taken 10 weeks after operation shows wound fully epithelialized.

Fig 4. A) Intraoperative photograph shows large (10-cm) wound and exposed temporalis muscle. B) Photograph taken 10 months after operation shows acceptable cosmetic result. Wound epithelialized in 8 weeks.



in other units (eg, scalp, forehead, and neck).

RESULTS

Among 185 patients with large full-thickness defects of the head and neck after Mohs surgery (112 men, 73 women), the mean age was 67 years (range, 35 to 91 years). The mean length of follow-up was 3.1 years (range, 6 months to 15 years). The majority of wounds healed within 8 weeks after surgery. When perichondrium or periosteum was removed, healing was significantly delayed and required as long as 18 weeks for epithelialization to occur. No wound infections were seen in this study.

Ear. As expected, through-and-through defects of the helical rim healed with a "cookie-bite" deformity and without spontaneous recontouring; reconstruction was necessary for patients who desired improved cosmesis. When the defect extends around the free edge of the helix and exposes cartilage denuded of perichondrium, the result is a floppy ear. This deformity was not noted in any of our study patients who had intact perichondrium on at least 1 side of the cartilage. Defects of the antihelix healed spontaneously with satisfactory cosmetic results unless cartilage removal resulted in contour deformities. When the helix and antihelix were both affected, the sulcus

was likely to become effaced. The skin of the entire concha could be removed with no or minimal (webbing) deformity (Fig 1). Stenosis of the external auditory canal was rarely observed (1/12, 8%), even for circumferential wounds. Similar results have been reported by others.⁵ Wounds of the posterior aspect of the ear healed well with minimal webbing, even when crossing the sulcus (Fig 2). This is the typical full-thickness skin graft donor-site defect.

Except for through-and-through defects of the helical rim, we allowed many wounds of the ear to heal by secondary intention and reserved surgery for unacceptable cosmetic results.⁶

Scalp. During our initial experience, surgery for large defects was performed to cover exposed bone and consisted of transposition skin flaps, transposition temporoparietal fascia flaps with split-thickness skin grafting, tissue expansion, and full-thickness skin grafting. These procedures were often lengthy, complex, and staged. Delays of several weeks or longer were required for bare bone to granulate sufficiently to support skin grafting. Scalp defects heal more rapidly with intact periosteum, but even wounds as large as 7 cm that were devoid of periosteum granulated well (Fig 3). If the bare bone was not granulating after several weeks, partial decortication was done

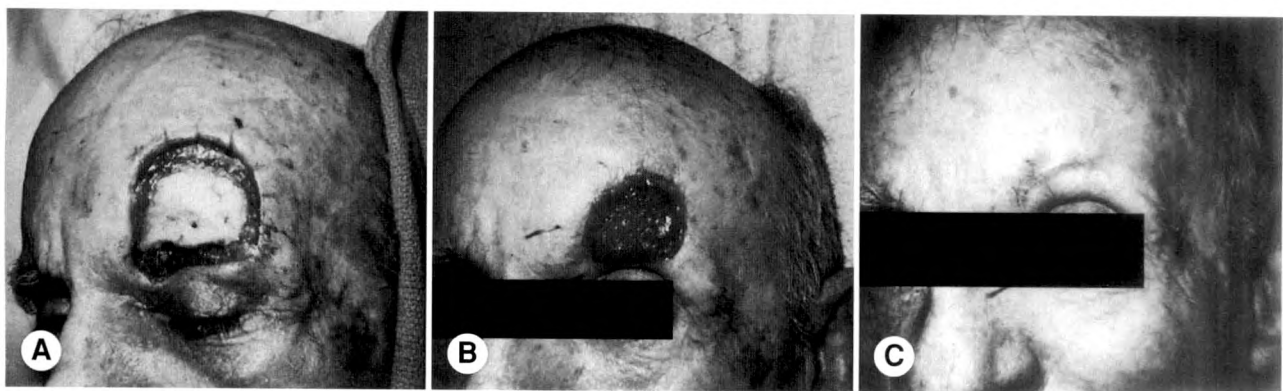


Fig 5. A) Intraoperative photograph shows 5-cm soft tissue defect with 4 cm of exposed bone denuded of periosteum and painted with 100% trichloroacetic acid. B) Photograph taken 5 weeks after operation shows defect completely granulated. C) Photograph taken 6 months later shows acceptable cosmetic result.

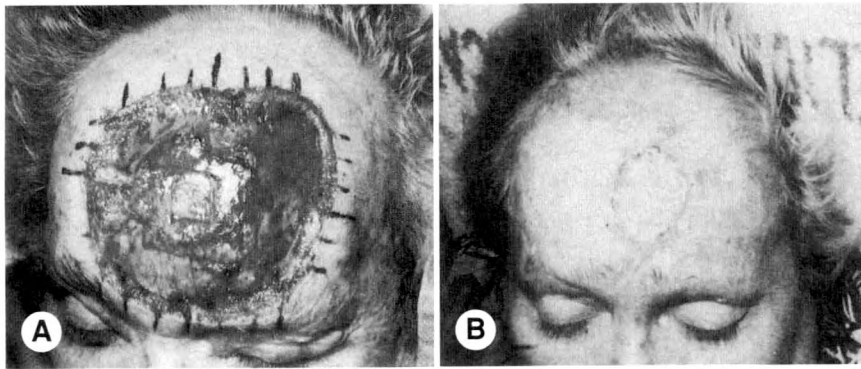


Fig 6. A) Intraoperative photograph shows large (10-cm) defect affecting forehead and exposing bone centrally. B) Photograph taken 3 months after operation shows skin graft prompted by delay in healing of central portion of wound.

to stimulate granulation. Desiccation necrosis was rarely observed and affected the outer table only.

Even large wounds reepithelialized rapidly when bone was not exposed (Fig 4). However, healing of wounds >10 cm in diameter was prolonged and tended to result in unstable epithelium in the center of the wound. If healing was delayed for more than several months, the residual defect underwent skin grafting. Scalp wounds that healed by secondary intention contracted about 50% and resulted in a flat or slightly depressed white scar.

When possible, scalp wounds were closed primarily. Other wounds were allowed to heal by secondary intention. Skin grafting was reserved for any area in which healing was delayed.

Forehead. As with the scalp, we initially used flaps, skin grafts, and tissue expansion to repair large defects, especially those that had bone exposed. Surgical closure often proved unnecessary: these wounds healed well by secondary intention, even when bone was exposed (Fig 5). When very large wounds (>10 cm diameter) resulted in delayed healing, the nonepithelialized central portion could receive a skin graft (Fig 6). Because lax, convex surrounding skin allowed contraction, temporal (8/11, 73%) and glabellar (4/4, 100%) defects often healed with favorable cosmetic results. Taut skin in the central forehead usually (11/19, 58%) resulted in a poor cosmetic re-

sult because of depressed scars.

We preferred to close wounds of the forehead at initial surgery if this could be done without the use of flaps or grafts. Wounds otherwise healed by secondary intention, with surgery reserved for unacceptable cosmetic results.

Nose. When allowed to heal by secondary intention, defects of the nasal tip and ala, because of their convexity, often resulted in unacceptable cosmesis (because of depressed scarring and alar retraction) and impaired function (difficulty breathing caused by alar collapse). Repair at excision or shortly thereafter with flaps or full-thickness grafts proved an appropriate option. Lesions located in the medial canthus area and along the nasal-cheek groove tended to heal with excellent cosmetic results when allowed to heal spontaneously. Defects on the dorsum healed with variable cosmetic results.⁷ Flaps and full-thickness skin grafts were placed in those patients in whom surgery was required. Patients whose skin defects affected most of the nose underwent reconstruction using forehead flaps or full-thickness skin grafting, usually within 1 month. Skin grafts healed well with minimal distortion and with pleasing cosmetic results (Fig 7). Large defects that healed spontaneously resulted in cosmetic and functional defects of the affected subunit, often with retraction, distortion, and breathing difficulty (Fig 8). This result was difficult to reverse with surgery.

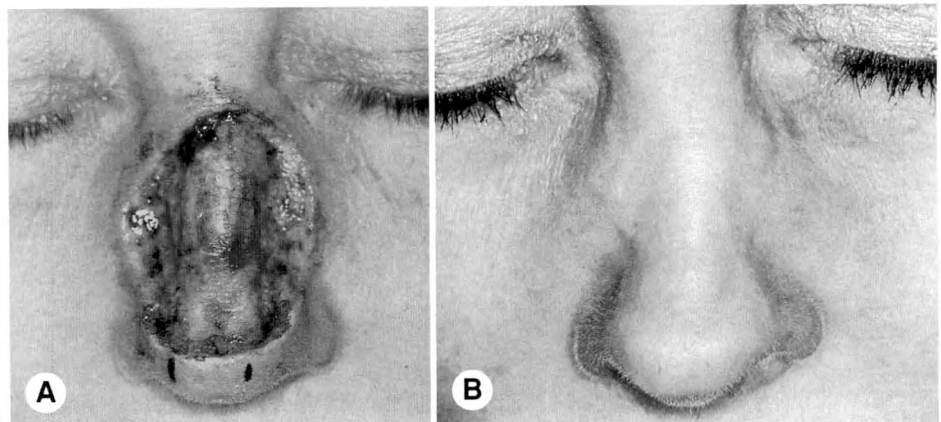


Fig 7. A) Intraoperative photograph shows large defect affecting skin of nose. B) Photograph taken 9 months after full-thickness skin graft shows good cosmetic result.

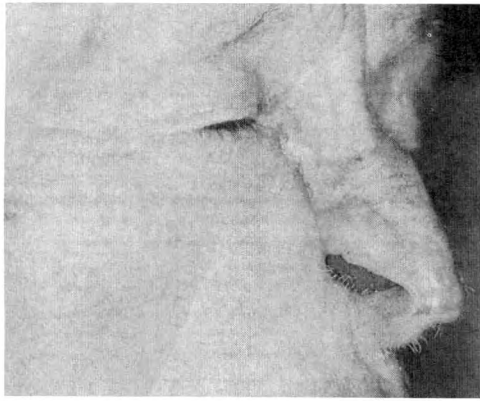


Fig 8. Photograph of large skin defect affecting nose shows unacceptable result 3 years after spontaneous healing. Note distortion with severe alar retraction.

We preferred to close a wound primarily if this could be done without producing excessive skin tension or distortion. Exceptions to this practice included wounds of the medial canthal area and nasal-cheek groove, which had excellent cosmetic results when allowed to heal by secondary intention. After suitable granulation developed, skin defects of the entire nose were repaired with full-thickness skin grafting.

Neck. The majority of large defects of the neck were located on the lateral or posterior aspect and were deep, thus requiring partial resection of the underlying muscle. Healing by secondary intention was prompt, occurred mainly by contraction, and yielded acceptable cosmetic results, ie, linear scars oriented along relaxed skin tension lines (Fig 9).

We closed defects that could be closed without the use of flaps or grafts and allowed large neck defects to heal by secondary intention. No undesirable cosmetic results were noted.

Cheek. Small defects in the nasolabial fold and nasal-cheek groove healed with excellent cosmetic results. Large defects tended to result in distortion, especially when located near the nose or lower eyelid (Fig 10). This distortion was sometimes tempo-

rary. We closed these defects by using a cheek-neck rotation flap or allowed them to heal by secondary intention and used surgery to correct any residual cosmetic deformity (Fig 11). Preauricular and infra-auricular defects healed well by secondary intention (Fig 12). Large central defects healed unpredictably, often (3/4, 75%) resulting in unsightly, white, atrophic scars. However, when the defect involves the eyelid or vermilion border, use of flaps or full-thickness grafting is required to prevent distortion. Split-thickness skin grafting usually led to a poor cosmetic result because of mismatched color. Sizable through-and-through defects (into the oral cavity) required flap closure.

Wounds extending to the eyelid, lower lip, or vermilion border are likely to cause distortion and are best repaired promptly. We preferred to allow large central defects to heal by secondary intention and to reserve surgery for unacceptable cosmetic results.

Lip and Chin. The majority (4/7, 57%) of large wounds of the chin healed with unsatisfactory cosmetic results when allowed to heal by secondary intention. Large superficial wounds healed with atrophic scarring, and large deep wounds (ie, those that exposed the periosteum) healed with retracted scarring (Fig 13).

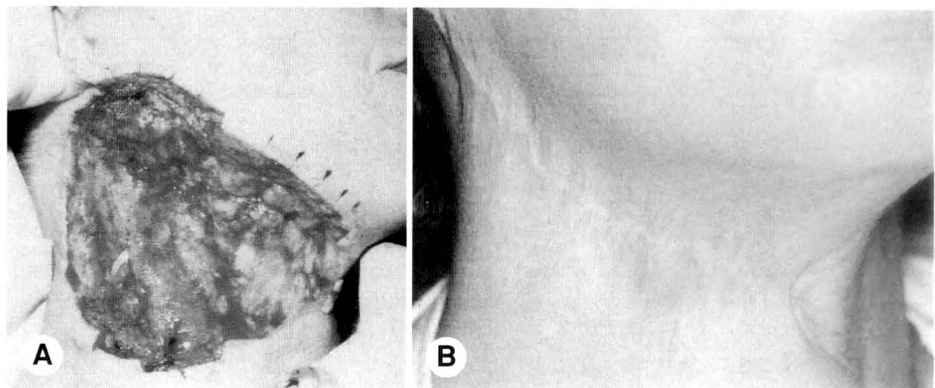
We did not study patients with carcinoma of the lip requiring wedge resection and repair. When not adjacent to the vermilion border, small defects of the alar base, nasolabial fold, and philtrum heal by secondary intention with acceptable cosmesis. Seventy-five percent (8/12) of wounds affecting both the skin and the vermilion border resulted in distortion, whereas the others healed with satisfactory cosmetic results (Fig 14).

As surgery for large defects of the skin of the lip or chin is often unsatisfactory,⁸ we allow wounds to heal by secondary intention and reserve surgery for repair of unsatisfactory results.

DISCUSSION

All full-thickness skin wounds heal by contrac-

Fig 9. A) Intraoperative photograph of 13-cm lateral neck defect shows partially resected underlying muscle and exposed spinal accessory nerve. B) Photograph taken 21 months after operation shows transverse linear scar and good cosmetic result. Defect epithelialized in 6 weeks.



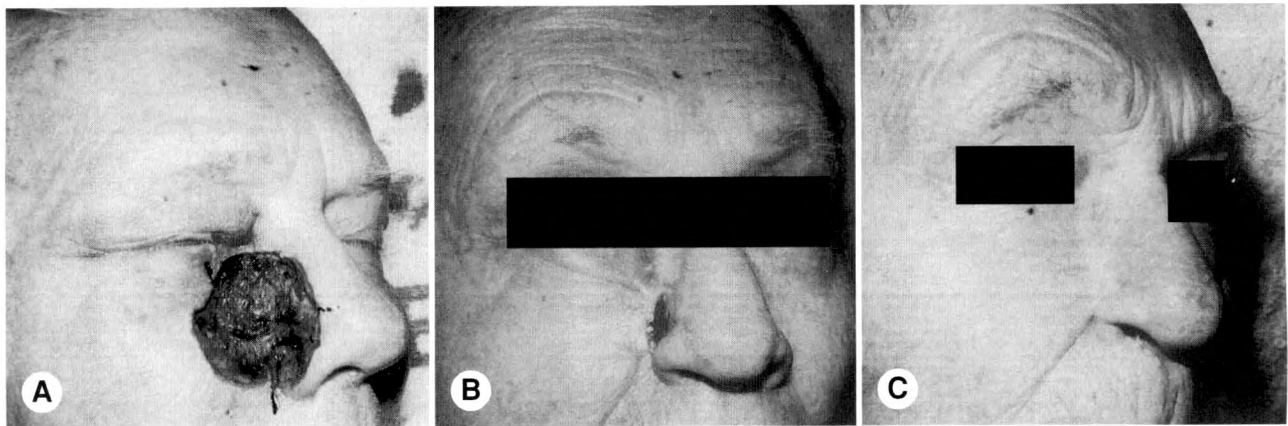


Fig 10. A) Intraoperative photograph shows defect of alar-cheek groove, including portion of eyelid and ala. B) Photograph taken 4 weeks after operation shows nearly healed wound with asymptomatic ectropion and alar retraction. C) Photograph taken 11 years after operation shows acceptable cosmetic result. Ectropion slowly resolved over several years, but alar retraction persisted.

tion and reepithelialization. Healing time is related to the logarithm of the wound area; therefore, regardless of size, most wounds that involve only the soft tissue heal in about the same amount of time. In our series, the majority of soft tissue wounds healed within 8 weeks. Healing is delayed by any process or event that decreases vascularization to the tissue (eg, smoking, but especially previous irradiation, surgery, or denuding bone or cartilage of its covering). When perichondrium or periosteum is removed, healing time doubles at a minimum. Wounds that heal mainly by contraction tend to have the most pleasing cosmetic result, because similar-appearing surrounding tissue is recruited into the defect. Uncontracted areas heal by reepithelialization, which often results in a depressed, hypopigmented atrophic scar devoid of dermal and adnexal structures.

Whether facial Mohs wounds are closed at initial surgery, closed sometime after surgery, or allowed to heal by secondary intention depends on the anticipated cosmetic and functional outcome of treatment.

We support the concept of allowing selected large defects to heal by secondary intention, reserving surgery for cases with an unacceptable outcome. We believe this is in the patients' best interest and do not allow the cost of a later restorative operation to bias our decision, because all costs are covered by the Kaiser Permanente not-for-profit system of care.

Zitelli⁹ was among the first to detail cosmetic results after spontaneous healing and noted that the most important predictor of cosmetic result is location. In general, wounds heal with a more favorable cosmetic result when located on concave surfaces of the face and neck. As Zitelli noted, small wounds in any subunit heal better than large and deep ones. This observation is less important for areas that consistently heal well, eg, the nasolabial fold and the preauricular area. Hypopigmented scars are less obvious in light-skinned persons. Lax skin, most often seen in aging patients, allows the wound to heal more by contraction and to be camouflaged by wrinkle lines.

Even though small defects may be surgically re-

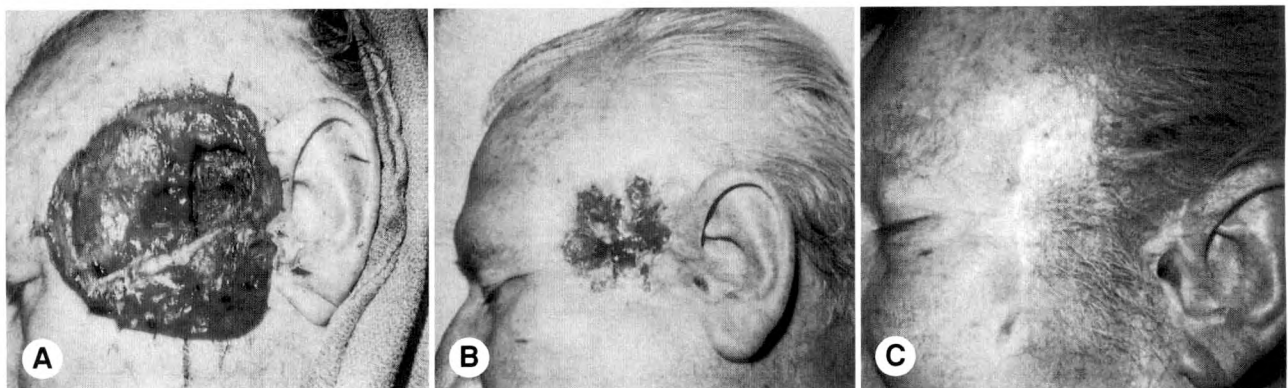
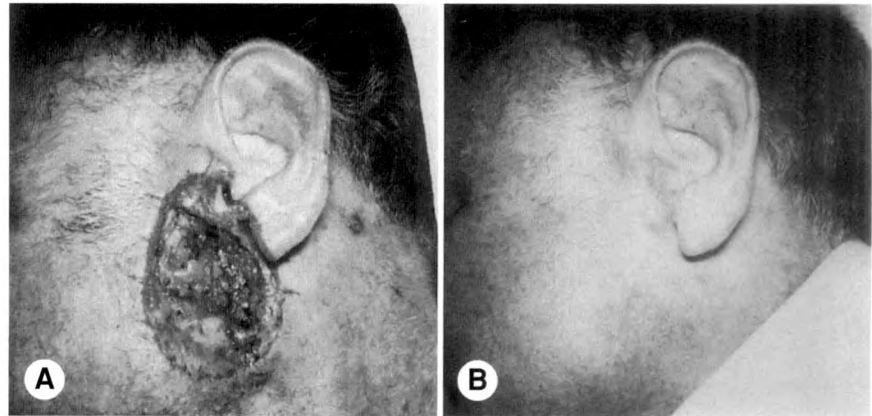


Fig 11. A) Intraoperative photograph of defect, 4.5 cm wide and 1.5 cm deep, affecting cheek and temporal portion of forehead shows partially resected temporalis and masseter muscles, as well as exposed zygomatic arch. B) Photograph taken 4.5 months after operation shows defect nearly epithelialized. C) Photograph shows result 3.5 years after spontaneous healing and subsequent surgical revision of residual scar.

Fig 12. A) Intraoperative photograph shows defect 6.5 cm wide and 1.5 cm deep (extending into parotid gland) and partially resected earlobe. B) Photograph taken 16 months after operation shows excellent result. Wound epithelialized in 7 weeks.



paired relatively easily, selected wounds may heal spontaneously with excellent cosmetic results. These wounds include those located in the nasolabial fold, alar base, glabella, medial canthus, nasal-cheek groove, and preauricular skin. Large wounds of the head and neck tend to require extensive and complex reconstruction that may require several stages and many months to complete. Accurately anticipating the cosmetic and functional results of allowing large wounds to heal by secondary intention would enable surgeons to tailor treatment most effectively for individual patients. Goldwyn and Rueckert¹⁰ were among the first to document the cosmetic results of secondary-intention healing of sizable facial skin defects and conclude that the cosmetic results of secondary-intention healing were often comparable to or better than those of flaps or grafts, and that later surgery, if needed, may be less complex than surgery done primarily. Panje et al¹¹ similarly concluded that delayed healing of large midfacial defects may allow simpler reconstructive procedures and produce acceptable cosmetic and functional results. As documented here, our experience shows that selected large wounds allowed to heal by secondary intention have satisfactory cosmetic and functional results.

We initially covered bare bone with flaps to avoid osteomyelitis and desiccation necrosis. We subsequently noted that bone granulates well and supports skin grafting, even when the bone is denuded of peri-

osteum. Depending on the size of the wound, complete granulation may take several months. If the bone is not granulating well after several weeks, granulation may be stimulated by using a bur, chisel, or gouge to decorticate the bone. Rarely, desiccation necrosis and sloughing occur in the outer cortex, after which granulation proceeds quickly. In a report of 91 patients who had facial or scalp bone exposed after Mohs surgery, Snow et al¹² determined that in scalp wounds stimulated to heal by chiseling, granulation requires a period of time (expressed in weeks) equal to twice the diameter of the exposed bone (expressed in centimeters), and that complete reepithelialization requires a period of time (weeks) equal to 3 times the diameter of the skin defect (centimeters). Our experience generally agrees with this formula.

As a general principle, we close all wounds at the time of surgery or shortly thereafter when this can be done without the use of extensive flaps or extensive undermining. If it is not medically contraindicated, all wounds, large or small, in areas that heal poorly are repaired with flaps or grafts at the time of Mohs surgery or shortly thereafter. This approach minimizes the time required for healing. If the wound is not closed at the time of Mohs surgery or shortly thereafter, the patient's medical and social situation, concern for cosmesis, ability for and commitment to wound care, and realistic expectations of corrective surgery are assessed to determine whether surgical

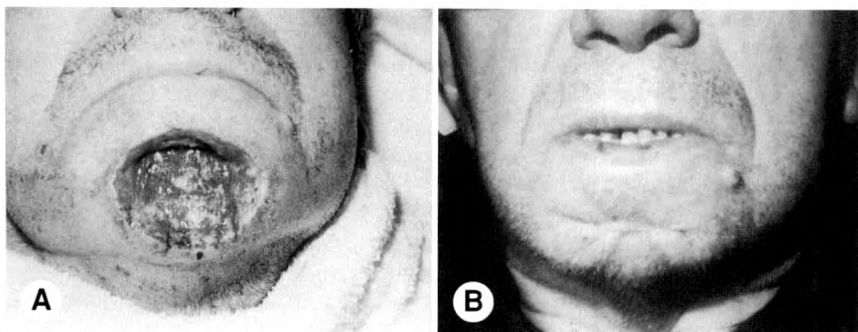


Fig 13. A) Intraoperative photograph of large 9-mm-deep defect affecting chin shows periosteum exposed centrally. B) Photograph taken 6 months after operation shows poor cosmetic result (ie, retracted scar).

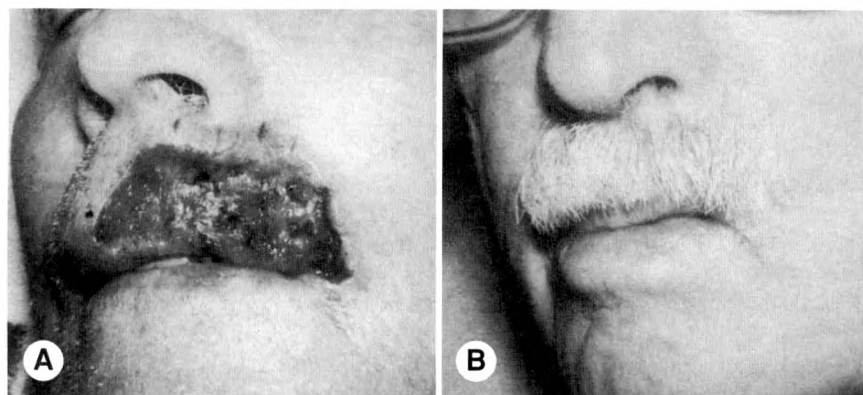


Fig 14. A) Intraoperative photograph of extensive defect of upper lip shows partially resected underlying muscle. B) Photograph taken 2 years after operation shows excellent result. Defect epithelialized in 6 weeks.

closure is appropriate. Alternatively, large wounds of the head and neck may be allowed to heal by secondary intention, with surgery reserved for an unacceptable cosmetic or functional result. This procedure is often less formidable than those done primarily.

If allowed to heal spontaneously, through-and-through defects of the ear do not regain contour sufficient to constitute an acceptable cosmetic result. Reconstruction is preferable for patients who desire it. When allowed to heal spontaneously, the majority of other skin defects of the ear heal with a pleasing cosmetic result, even after denuding of perichondrium. Defects on the posterior side of the ear heal well, with minimal or no webbing, even when they cross the postauricular crease. We allow these wounds to heal by secondary intention, unless they are small and easily closed.

When skin is removed from the entire nose, healing by secondary intention results in retraction, in distortion, and often in breathing difficulty after alar collapse. Although various methods of repair have been described here, we usually favor full-thickness skin grafts, because this procedure is relatively sim-

ple, the graft usually remains viable, and the cosmetic and functional results are good.

Neck wounds, even when affecting muscle and exposing nerves, usually heal with excellent cosmetic results. A linear scar is usually seen oriented along relaxed skin tension lines. Compared with defects of the face and scalp, little has been written about managing defects of the neck, probably because skin cancer of the neck occurs infrequently and because closing small defects is relatively simple.

Preauricular and infra-auricular wounds heal with minimal scarring. However, centrally located wounds usually heal with depressed, wide scars and may temporarily or permanently distort surrounding structures (eg, eyelids, ala, vermillion border). Early surgery should be performed if distortion is anticipated. The remaining wounds heal by secondary intention, and surgery can be reserved for unacceptable cosmetic results.

CONCLUSION

We support the concept of selective management of Mohs wounds through accurate prediction of the final cosmetic and functional result.

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TREATMENT OF NASAL POLYPOSIS IN BYZANTINE TIMES

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The goal of this study was to describe the therapeutic methods and surgical techniques used during Byzantine times (AD 324-1453) for a disease that has occupied physicians since antiquity: nasal polyps. The original Greek-language texts of the Byzantine medical writers, most of which were published after the 17th century, were studied in order to identify the early knowledge of the definition, symptoms, conservative treatments, and surgical intervention in cases of this disease. A considerable number of conservative treatments, etiologic and local (with inunctions or blowing of caustic substances), with evident influence from Roman medicine, were identified even in the early Byzantine medical texts (4th century). Further, some surgical techniques were described that seem to constitute evolution of the Hippocratic tradition. From the study of the original texts of Byzantine medical writers, their interest in the rhinological diseases is evident; in the case of nasal polyps, new techniques were mentioned. The first meticulous intranasal surgical removal of polyps was described. These techniques, obviously developed during the Hellenistic period, initially influenced European medicine and later the rest of the world.

KEY WORDS — ancient medical instruments, Byzantine medicine, history of rhinology, nasal polyps.

INTRODUCTION

In Byzantium, the successor of the Roman empire and the political, cultural, and scientific center of the Western world from 324 until 1453, when it fell to the Turks, talented physicians paid considerable attention to diseases of larynx, pharynx, nose, and ears. Some of them were specializing in these from early times, as an extract of Ulpian (AD 170 to 228), included in the *Pantect*, the well-known Byzantine collection of laws, reveals.¹ The contribution of the Byzantine period to the history of otorhinolaryngology is considerable, because the physicians of that era preserved in their texts accounts of important pharmaceutical treatments and surgical operations of the celebrated ancient Greek physicians.² The works of the eminent Byzantine physicians, such as Oribasius (4th century), Aetius of Amida (6th century), Alexander of Tralles (6th century), Paul of Aegina (7th century), Leon the Iatrosophist (9th century), Theophanes Chryssovalantes (10th century), Michael Psellus (11th century), Nicolaus Myrepsus (13th century), and Ioannes Actuarius (14th century), contain extensive chapters concerning otorhinolaryngological topics.^{1,3}

In the field of rhinology in particular, Byzantine physicians provided meticulous treatments for the disease of inflammation (rhinitis), ozena and nasal malodor, ulcers, anosmia, epistaxis, polyps, cancer, bruises, and fractures. Some of these physicians de-

scribed special surgical techniques for some nasal diseases, and especially for the removal of polyps and reconstruction of the nose in cases of defects and fractures.⁴ Because most of them, especially in the early period (4th to 7th centuries), were trained in the famous Medical School of Alexandria, they followed Hippocratic, Hellenistic, and Roman traditions and compiled accounts from the relevant texts — many of them now lost — enriching medical science with their wealth of experience.²⁻⁴

Because only some incomplete descriptions of these topics are known in modern bibliography, usually quoted from translations,⁵ a new presentation of the methods of pharmaceutical and surgical treatments of polyps, based on direct translations from the original Byzantine medical texts, might prove useful for understanding the philosophy and techniques of our predecessors and the roots of modern rhinology.

MATERIAL

Definition and Etiology. Aetius, giving a description of polyps, considers that they resemble the color and composition of the sea creature with the same name, and he adds that they are caused by thick and gluey humors descending from the head.⁶

Paul of Aegina begins his chapter "About Polyps" with a definition of the disease.^{7,8} The polyp, according to him, "is a tumor which is created in the nose

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and which takes its name from the marine animal because it resembles the flesh of this creature and its behaviour; as the animal protects itself with its tentacles, so the polyp reacts and extends itself in the nose of a sufferer, obstructing the nostrils and provoking dysfunction in breathing and talking."^{7(p144),8(p64)} The same opinion is later expressed by Theophanes Chrysovalantes (incorrectly known until recently as Nonnus).⁹

Ioannes Actuarius describes the tumor as a "hypersarcoma which obstructs the ethmoid openings and often spreads to the nearby openings of the nose and prevents inhaling and exhaling and the excretions of the nose."^{10(p449)}

Conservative Treatment. Oribasius first uses several substances, such as anemone or a mixture composed of grated myrrh, incense, egg white, and snails, applied to the head for 9 days as poultices.¹¹ After this, local treatment follows. He recommends inunctions using a feather to apply caustics that slowly devour polyps. For this purpose, he prescribes chyle of apples of cypress, roots of the herb dracontion, and other herbs or a caustic solution of quicklime, copper, niter, and alum dissolved in lime water.¹² The writer also suggests blowing various substances into the nose with a straw. Among these are flowers of copper, alum, iron, myrrh, incense, and the herb aristolochia. He further uses a chyle of chopped pomegranate that is boiled in a tin container so that it will be solid enough to be kneaded in particles that will be appropriate to insert into the nose. If the polyp is located deeper in the nose and can be easily approached from the mouth, Oribasius recommends inunctions of several dry drugs on the palate with feathers¹¹ or using a probe (specillum) called a milotris,¹³ the end of which is wrapped in wool.

Aetius believes that the treatment must be first etiologically based on the drying out of the head with poultices or inunctions, especially on the temporal area, after previously completely shaving the head, and local treatment follows.⁶ He, therefore, applies, along general lines, the same treatment as Oribasius. Aetius also uses a powder of alum, myrrh, sanda-

rach, and copper that is inserted into the nose with a probe, after previously cleansing the nostrils with an infusion of aromatic wine. Another drug is alum with flowers of copper, which are dissolved in strong vinegar in a copper container left in the sun on a very hot day until the drug is dried out; then it becomes powder and is blown into the nostrils with a straw while the patient keeps his or her mouth full of water.

Aetius also suggests, for cauterization of persistent polyps, strong caustics, mainly with mustard seed, which is pounded in water and then forms small grained pieces.⁶ This drug is inserted into the nose after previously wrapping it in a piece of material, the beginning of which is left outside the nose so that it can be pulled out and removed after 1 day. Aetius confirms that polyps are easily removed with this treatment.

Aetius also conveys to us a series of local treatments, either blowing or inunctions using a probe, taken from the ancient physicians Apollonius (1st century BC), Asclepiades from Bithynia (1st century BC), and Antipater and Galen (2nd century AD).⁶

The meticulous directions of Aetius even reach the point of his suggesting a special drug that contains dry rose petals for "eunuchs who have a softer-textured body and are considered more sensitive."^{6(p241)} He also confesses that in a drug administered to a rich man he added old aromatic wine "because the patient demanded it."^{6(p241)}

Surgical Intervention. Paul of Aegina recommends the removal or cauterization of polyps with iron cauteries.^{7,8} The writer classifies polyps as operable and inoperable. Hard, rigid, and almost black polyps are considered to be malignant because they have become cancerous and must not be operated on; on the other hand, fragile, spongy, and noninvasive polyps are not malignant and must be operated on.

For polyp removal, the patient is placed in a seated position exactly opposite to the sunlight. With the left hand the nostril is opened wide, while with the right hand, using the myrtle leaf-like sharp point of the "polypodic sword" (polypus knife; Fig 1A¹³), the



Fig 1. A) Polypodic sword (polypus knife). B) Polypoxestes (polypus eradicator). (Reprinted with modifications.¹³)

physician cuts the polyp at its base attached to the nose. Then he uses the other end of the same instrument, which consists of a basket (scoop), to pull out the flesh that has already been undermined. If the nostril is clear, conservative treatment is continued. If, however, parts of the polyp have remained, these are cleared with another instrument called a "polypoxystes" (polypus scraper, polypus eradicator; Fig 1B); the remaining parts are then removed with vigorous scraping and twisting.

After the operation, infusions of oxycraton (a solution of vinegar and milk) or wine are made into the nose; if the liquid flows through the palate to the pharynx, it means the operation was successful,^{7,8} otherwise, the "sawing" method follows.

In the sawing method a linen thread of medium thickness is taken and knots are tied at a distance of 2 or 3 fingers apart. The thread is then introduced into the opening of a double-headed probe (specillum). Then the other end of the probe is introduced into the nose, and via the nasopharynx it comes out through the mouth; each end of the thread is grasped and, with a push-and-draw movement, as if one were sawing, the fleshy polyps are rubbed away.

After this operation the opening of the nose must not be allowed to close, and for this purpose a piece of wadding that is formed like the wick of a lamp is used. After the third postoperative day, the "trochiski" (pills) of Antonius Mussa (a Roman physician of the 1st century AD) or other similar medicaments that dry the area are given. Later, healing "trochiski" are taken, and if necessary, lead tubes are placed into the nose to prevent closure.^{7,8}

The malignant inoperable tumors, according to Paul, are cauterized with olivary cauteries.^{7,8}

Physicians later followed approximately the same conservative and surgical treatments described above. Leon the Iatrosophist recommended only surgical intervention,¹⁴ either with the appropriate instrument (polypus knife) or with the "sawing" method described by Paul of Aegina.

Theophanes Chryssovalantes suggested only conservative treatments similar to those of Aetius with blowing or inunctions.⁹ He followed the etiologic approach that Aetius had propounded, and for that reason recommended purgation of the whole body.

The famous physician and pharmacologist Nicolas Myrepsus¹⁵ (13th century) followed the prescriptions of Aetius, applying caustic powders locally.

DISCUSSION

Nasal polyposis seems to have occupied the Byz-

antine physicians from very early times; they tried to explain its cause and to apply the appropriate treatment.

Oribasius, from the 4th century, had already provided a series of conservative treatments,^{11,12} without mentioning surgical intervention, although he was a renowned surgeon and preserved some ancient techniques such as those for aneurysms,¹⁶ tracheotomy,³ and plastics of the face (rhinoplasty, etc), thus influencing later European medicine.⁴

Aetius (6th century), on the basis of Oribasius' text and the works of a considerable number of ancient Greek physicians, also followed conservative treatment, aiming, as he maintained, to avoid surgery or cauterization.⁶ This remark indicates that he had knowledge of earlier surgical techniques. His conservative treatment is classified as local on the polyps and as general on the head. The former treatment had the aim of slowly dissolving the mass of polyps with caustics, a method meticulously described by Oribasius in early Byzantine times.^{11,12} He also adopted the general treatment of Oribasius and explained its etiologic role: to dry the excretions descending from the brain to the nose. It sounds curious today, but it may be completely understood if we have in mind that according to contemporary anatomic belief, liquids from the brain were thought to come down to the nose through small pores of the scleromeninx. This meninx was believed to be directly attached to the ethmoids, which are perforated with small pores (in Greek the word ethmoid means like a strainer). The excretions from the brain, passing through these filters, were believed to reach the nostrils.¹⁷

The conservative treatments of Oribasius and Aetius, aimed at devouring of the polyps by caustics, are quoted from the works of Galen, who first used similar substances, such as dracontion, pomegranate, copper, and sandarach, blowing them into the nose or applying them, using a probe wrapped with wool.^{18,19} It is evident that Oribasius and Aetius copied this knowledge from the works of Galen, but added new information and personal observations.^{6,11,12}

Cauterization with iron cauteries, practiced by Byzantine physicians, was obviously inspired by Hippocratic, Hellenistic, and Roman medical sources.

The surgical techniques, however, meticulously described only by Paul of Aegina, constitute evolution of the ancient techniques and are unique in the Byzantine medical bibliography.

It is well known that the surgical treatment of polyps had occupied the Hippocratic physicians (5th century BC). They had described nasal polyp removal techniques in some books of the "Corpus Hippocra-

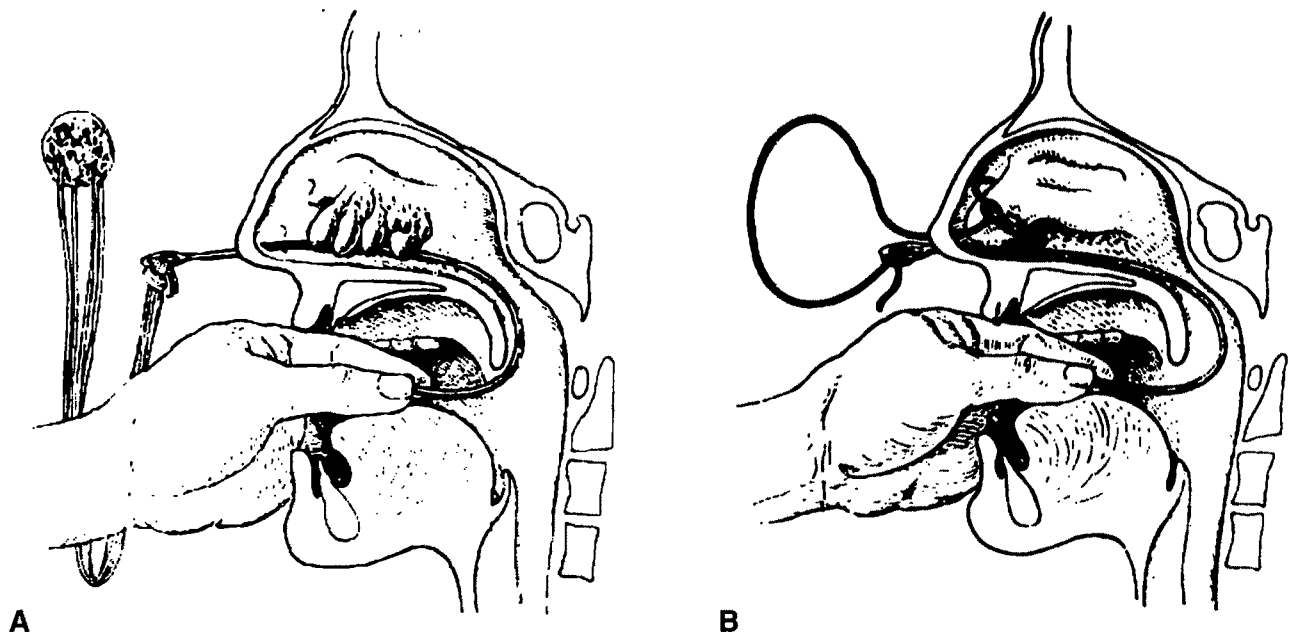


Fig 2. Hippocratic techniques for polyp removal. A) "Sponge" technique. B) "Loop" technique. (Reprinted with modifications.⁵)

ticum."⁵ The writer of the work "Diseases II" (perhaps Draco or Thessalus, sons of Hippocrates) devotes an extensive analysis to the surgical removal and cauterization of polyps.^{20,21} He remarks that a polyp forms in the nose and "hangs down from the central cartilage like a uvula."^{20(pp246-7)} It has a soft consistency, and during breathing, the polyp moves in and out of the nostril. It affects the tone of the voice and causes snoring.

Hippocratic Techniques. The Hippocratic writer recommends 2 methods of surgical removal: the "sponge" and "loop" techniques.^{20,21}

In the "sponge" technique, a sponge is made spherical like a ball and is wound with a cord of Egyptian linen so that it is hard. The size is relative to the opening of the nostrils. Then the sponge is bound with threads a cubit in length, in 4 places. The threads are passed through the loop end of a flexible tin curette. The other end of the curette is inserted into the nose until it reaches the mouth and is drawn out of the mouth; then, placing a bifurcated guide under the uvula as a support, the physician avulses the polyps through the mouth, pulling the threads (Fig 2A⁵).

The second method, the "loop," is described in cases of spherical soft polyps projecting into the nasal cavity. In this technique, a small noose is made with a fibrous cord wrapped in fine linen. The other end of the cord is passed through the loop end of a tin curette that is directed through the nose to the mouth (Fig 2B). Then the noose is placed into the nostril, adjusted, and stretched over the polyp by means of a bifurcated guide. Then, using a support under the uvula, the physician avulses the polyps,

pulling the cord through the mouth. These Hippocratic techniques were used in Europe until at least the 19th century.⁵

Further, the Hippocratic writer describes open surgical intervention in a case of a hard polyp "making a sound like a stone"^{20(pp250-1)}; by performing an incision of the skin of the nostrils externally with a scalpel, the polyps are removed and then cauterized. Then the wound of the incision is stitched together and is healed with ointment. It seems that this may be a case of a rhinolith and not of real polypectomy.

The same writer, in another case of a hard polyp, proceeds to cauterization with 3 or 4 irons through a syringe that is used as a protective tube to avoid burning of the nearby nasal area.^{20,21} The treatment is completed with powder of black hellebore.

It is very possible that all these cases of polyps referred to by the Hippocratic writer are not polyps but might be other forms of tumor, perhaps cancer; he refers in particular to "some forms of cancer present on the end of the nasal cartilage which must always be cauterised."^{21(pp200-1)}

Roman Techniques. Celsus (1st century AD) believes that polyps are a form of tumor, white or reddish, attached to the bone of the nose, filling the nostrils and extending toward the lips and backward toward the mouth, causing problems of breathing.²² They are usually soft but are sometimes very hard and are thought to be cancerous. The Latin writer expresses views about the surgical operation of these tumors similar to those of Byzantine writers, believing that the malignant form is inoperable.²² For the

soft benign polyps, he prefers surgical removal with a lancet with a sharp spearhead, taking care not to damage the cartilage under it.²³ After the detachment of the polyp, it is extracted by an iron hook. Then the nostril is gently filled with folded lint to stop the bleeding. The healing process is continued with application of medicaments.

In cases of cancerous tumors, Celsus prefers the application of caustics to dry up the tumor.²² He prescribes a drug consisting of minium from Sinope, copper ore, lime, and sandarach that is inserted into the nostril with the use of lint or a feather.²²

The similarities in the therapy described in Celsus' work to those of the Byzantine texts are due to the fact that all the eminent Byzantine physicians had studied in the famous Alexandrian Medical School, and Celsus had used a considerable number of medical sources derived from the Hellenistic period.²⁴

A century later, Galen refers to the removal of polyps with a "narrow small lancet, completing the procedure with cleaning the roots of the polyps with a scraper."^{25(p785)} He does not give any further information (there may have been a detailed description in his lost book about surgery), but probably the method is the same as that described later by Paul.

In conclusion, the treatment of nasal polyps during the Byzantine period was conservative (etiologic and local with caustic substances) and surgical. The Byzantine physicians followed the pharmaceutical treatments of ancient Greek physicians, mainly those of Galen, and practiced surgical methods resembling those of Hippocratic tradition, such as the "sawing" technique and cauterization, but also introduced conventional surgical techniques. The description of the intranasal removal of polyps by Paul of Aegina is unique in the medical Byzantine bibliography, and

more meticulous and understandable than the similar brief one of Celsus and Galen. The hypothesis that this method developed during the Hellenistic period (3rd century AD), when anatomy and surgery flourished, appears rational, as it is completely unknown in the Hippocratic bibliography and was briefly mentioned by Celsus and Galen in the Roman period.

The development of special delicate instruments (such as the polypodicon sword and polypoxestes) during the Hellenistic and Roman periods^{13,26} certainly improved intranasal surgical techniques. Further, the fact that the Byzantine doctors were not only compilers of the ancient texts, but gifted physicians possessing wide practical experience, as is evident from their many personal additions to the ancient texts,^{16,27} is obvious in Oribasius' and Aetius' extracts. It is well known that Byzantine medicine influenced European medieval medicine during the Salernian period.²⁴ Bruno da Longoburgo (13th century) employed a technique following that of Paul of Aegina, as he conveys in his *Chirurgia Magna*.²⁴ Rudolph Voltolini practiced the ancient Greek techniques for the removal of polyps until the 19th century,⁵ and perhaps other physicians were aware of these, among them the inventors of new instruments such as G. Falloppius, who devised a polyp snare, and Fabricius ab Aquapendente, who employed a so-called forceps (angulated scissors).²⁴ Recent research discovered that rhinoplasty was also transmitted from Byzantium to Italy and influenced modern European surgeons.⁴

The treatment, therefore, of polyps in Byzantine times seems to represent a further paradigm of the ancient Hippocratic, Hellenistic, and Roman traditions that later were transmitted to and influenced European rhinology, constituting remarkable roots of the modern methods of confrontation.

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IMAGING CASE STUDY OF THE MONTH

MENINGITIS DUE TO ACUTE OTITIS MEDIA AND ARACHNOID GRANULATIONS

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INTRODUCTION

Arachnoid granulations (AGs) are structures through which cerebrospinal fluid (CSF) drains from the subarachnoid space into the intracranial venous system.¹ Histologically, they appear as herniations of the subarachnoid space into the dura mater.¹ They penetrate the sagittal sinus and the lacunae laterales primarily; however, they may be located off the midline and contact bone. They have long been known to cause erosion of the inner calvarium² when they do not contact a venous structure. Gacek³ first introduced the concept of spontaneous CSF otorrhea being due to posterior fossa AGs. Gacek identified an 8.5% incidence of AGs in the posterior fossa of the temporal bone,³ while others have found up to a 22% incidence in the tegmen tympani.⁴ Gacek postulated that the majority of cases of "spontaneous" CSF otorrhea that had been reported to date were in fact due to these bony defects. The AGs are known to enlarge with age, eventually eroding bone if not within the lumen of a venous structure. With normal daily increases in CSF pressure, further bony erosion takes place. Once the AG has eroded into the air cell system, CSF otorrhea is possible; alternatively, as in our case, it may be the entry point for bacterial invasion.

CASE REPORT

A 46-year-old woman with no otologic history was found to have otitis media by her local physician and treated with oral antibiotics. Within 24 hours, she was found unresponsive by her family and was taken to the emergency department. She responded only to painful stimuli and was immediately intubated. Examination was remarkable for a bulging, erythematous tympanic membrane on the left side. A myringotomy and tympanostomy tube insertion was performed, and a specimen was sent for a Gram stain

and culture. Additionally, cultures were obtained from the blood, urine, sputum, and CSF. Gram stains from both the lumbar puncture and tympanocentesis revealed gram-positive cocci in pairs. The CSF cell count demonstrated 4,350 white blood cells per cubic millimeter, 1,350 red blood cells per cubic millimeter, a glucose concentration of 2 mg/dL, and a protein concentration of 512 mg/dL. The patient was subsequently admitted to the medical intensive care unit with the presumptive diagnosis of otitic meningitis and begun on triple antibiotic therapy (vancomycin hydrochloride, ceftriaxone sodium, and metronidazole).

A high-resolution computed tomography (CT) scan of the temporal bones revealed a defect in the posterior fossa plate of the left temporal bone (consistent with an AG) and an opacified middle ear and mastoid (Fig 1). The AG had created a small bony defect in the posterior fossa plate. No evidence of chronic otitis media or abscess formation was identified. The inner ear revealed no signs of dysplasia, nor was there any evidence of underlying hydrocephalus. The contralateral ear was normal. Blood and CSF cultures grew *Streptococcus pneumoniae*, and the otorrhea demonstrated mixed *Staphylococcus* and *Streptococcus* species. The patient was unresponsive for the ensuing 4 days, and a repeat high-resolution CT scan was performed without additional findings. On the 5th hospital day, the patient began to open her eyes and respond to commands. By the 7th day, the patient was oriented to person and place and was subsequently extubated. Ophthalmologic evaluation demonstrated a left 6th nerve paralysis and multiple retinal hemorrhages, consistent with severe meningitis. By the 10th hospital day, the patient was afebrile. She completed a 2-week course of intravenous antibiotics.

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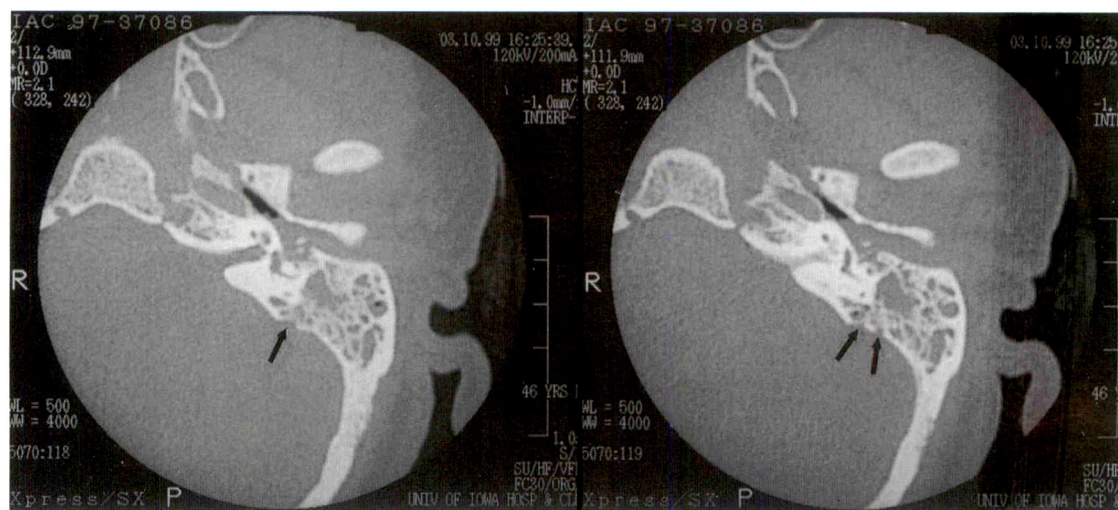


Fig 1. High-resolution axial computed tomography (CT) scan of 2 adjacent slices of left temporal bone without contrast. Note bony dehiscence of posterior fossa cortex anterior to sigmoid sinus (arrows). Absence of any signs of coalescence or cholesteatoma suggests that arachnoid granulation is responsible for defect. Patient also has mastoid and middle ear opacification due to acute otitis media. Fluid in external auditory canal is secondary to prior placement of tympanostomy tube.

Because of the presumed etiologic mechanism for her meningitis (AGs), the patient underwent a complete mastoidectomy for repair of the dural defect to prevent recurrence. Two small (<3 mm) AGs were identified in the posterior fossa, within the sinodural angle (Fig 2). Each defect was debrided of arachnoid and repaired with a fascia graft. The repair was reinforced with an inferiorly pedicled muscle flap. The patient's postoperative course demonstrated recovery of her initial conductive hearing loss and improvement in her speech discrimination by 16%. She has a persistent right 6th nerve palsy that is slowly improving.

DISCUSSION

Three clinical scenarios may occur after AG inva-



Fig 2. Operative photograph demonstrates dural defect in sinodural angle with arachnoid granulation visible in air cell system (black arrow). Left ear is in surgical position. White arrows mark superior and inferior limbs of posterior semicircular canal.

sion into the mastoid cortex⁵: 1) middle ear effusion, 2) septic meningitis secondary to acute otitis media, or 3) intracranial extension from chronic mastoid disease. Far and away the most common clinical picture is that of persistent middle ear effusion, which may or may not eventually lead to meningitis. Gacek³ identified a case of meningitis secondary to acute otitis media without apparent CSF otorrhea in a temporal bone specimen (postmortem). A Medline search has failed to reveal another case in the English-language literature in which meningitis was attributable to acute ear disease and an AG.

The diagnosis rests on the clinical picture, in addition to the appearance on high-resolution CT. Characteristic of AGs on CT is a punched out-like bony defect within the cortex, possibly extending into the mastoid air cell system.⁶ Magnetic resonance imaging demonstrates an intensity similar to that of the CSF in all pulse sequences.⁶ Treatment of AGs that cause CSF otorrhea involves either a mastoidectomy (posterior fossa defects) or a middle cranial fossa craniotomy (tegmen tympani defects) with closure of the dural defect with a fascia plug. In the middle fossa, a piece of bone should be placed over the tegmen defect, whereas in the mastoid, reinforcement with a muscle pedicle flap is sufficient. Management of meningitis and mastoiditis takes precedence over treatment of the AG until the patient's condition has stabilized.

Although uncommon, the occurrence of meningitis associated with acute otitis media should be suspected as indicating an underlying dural defect and an AG.

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IMAGING CASE STUDY OF THE MONTH

MALIGNANT TRITON TUMOR OF THE ETHMOID SINUS AND NASAL CAVITY

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INTRODUCTION

In 1932, Masson¹ first described a lesion that consisted of a malignant schwannoma with rhabdomyoblastic differentiation. Subsequently, Woodruff et al² coined the term "Malignant Triton Tumor" (MTT) to indicate such a neoplasm. The name refers to Locatelli's experiment in which a sciatic nerve implanted onto the back of a Triton salamander caused the growth of a supernumerary limb made up of neural and muscular tissue.³ Approximately 15% of MTTs contain additional mesenchymal or epithelial elements and are therefore designated as having "pluridirectional differentiation."⁴

Out of a series of 51 benign and malignant lesions of the sinonasal tract or nasopharynx treated by an endoscopic approach in the period January 1992 to December 1999 (Table 1) at the Department of Otolaryngology, University of Brescia, we herein report the case of an 81-year-old woman with an MTT of the nasal-ethmoid complex who is currently free of disease 36 months after surgery. A review of the literature that focuses on incidence, histogenesis, diagnosis, biological behavior, and treatment of MTTs

of the sinonasal tract is also included.

CASE REPORT

An 81-year-old woman was admitted to the Department of Otolaryngology of the University of Brescia with a history of right nasal cavity obstruction lasting several years, hypertension, and diabetes mellitus. Three times previously, she had undergone removal of polyps from the right nasal cavity under local anesthesia, without histologic examination. On endoscopy, the right nasal fossa was completely filled by a rose-gray, soft mass that apparently originated from the middle turbinate. An enhanced computed tomography (CT) scan confirmed the presence of a lesion that entirely filled the nasal cavity and the ethmoid sinus, protruded into the nasopharynx, and was characterized by a nonhomogeneous density. The maxillary, frontal, and sphenoid sinuses were opacified, suggesting the presence of an inflammatory fluid collection. A marked bony thickening of the ethmoid septa and middle turbinate was also evident, together with a small dehiscence in the midportion of the fovea ethmoidalis. There was no extension of the tumor to the orbit or to the contralateral nasal cavity (Fig 1). The patient refused magnetic resonance imaging (MRI). A biopsy specimen was obtained, and a diagnosis of malignant schwannoma with rhabdomyoblastic differentiation was rendered. The family history and an objective examination were negative for neurofibromatosis type 1 (NF-1), so no further radiologic examination was performed. The findings of routine blood tests, urinalysis, and a chest X-ray were within normal limits.

Two surgical options were offered and discussed with the patient: craniofacial resection and endoscopic removal. She elected to undergo the latter. With the patient under general anesthesia, the tumor was first debulked to allow access to some important sur-

TABLE 1. SUMMARY OF SINONASAL AND NASOPHARYNGEAL NEOPLASMS TREATED BY ENDOSCOPIC SURGERY (N = 51)

<i>Neoplasm</i>	<i>No. of Patients</i>
Inverted papilloma	21
Angiofibroma	13
Osteoma	5
Adenoid cystic carcinoma	2
Esthesioneuroblastoma	2
Plasmacytoma	2
Transitional cell carcinoma	2
Adenocarcinoma	1
Basaloid squamous cell carcinoma	1
Hemangiopericytoma	1
Malignant triton tumor	1

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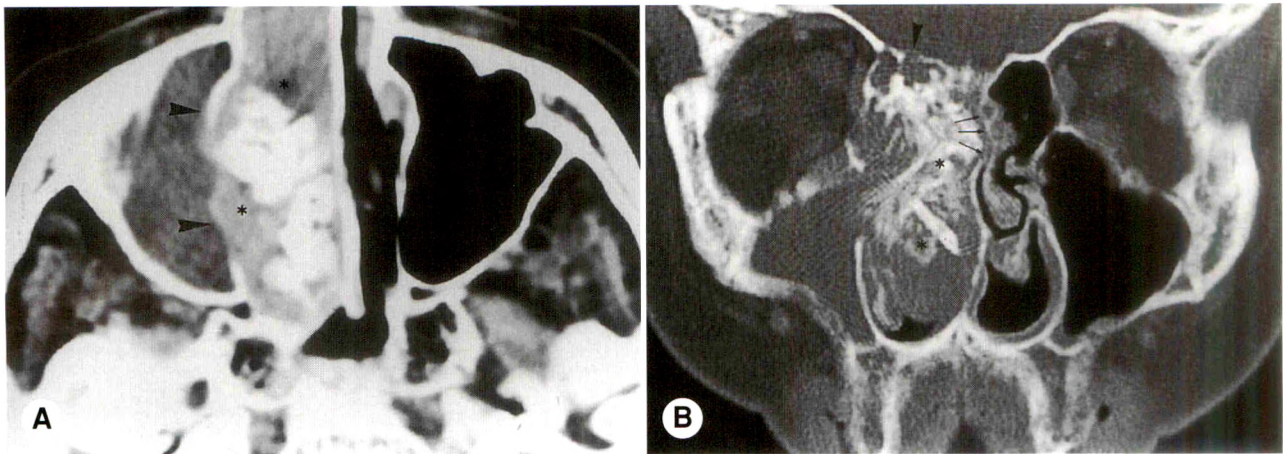


Fig 1. Computed tomography scans. A) Axial plane. Right nasal fossa is filled by solid mass enhanced after contrast agent administration (asterisks). Lesion entirely surrounds dense and irregular structure resembling abnormal middle turbinate. Middle antral wall has been displaced by lesion (arrowheads), and dehiscence areas are seen at middle third. B) Coronal plane. "Bone" window enables detailed evaluation of bone structures. Mass occupies right ethmoid sinus and projects into nasal fossa. It extends mostly along vertical framework of middle turbinate. In fact, only minimal displacement of lamina papyracea and of perpendicular lamina, which is partially eroded (arrows), can be observed. Right fovea (arrowhead) is also displaced and shows areas of erosion. One main finding of lesion consists of marked and irregular diffuse thickening of right middle turbinate (asterisks), which is rather enlarged and dense.

gical landmarks: the uncinate process, the root of the middle turbinate, the nasal septum, and the choana. After submucosal infiltration with 1% mepivacaine hydrochloride with 1:200,000 epinephrine, an incision was made along the area anterior to the uncinate process, going up to the agger nasi and the roof of the nasal cavity anteriorly to the cribriform plate, and down to the adjacent nasal septum. The dissection then proceeded laterally in an anteroposterior direction to expose the maxillary sinus, which was filled by a dense inflammatory secretion and apparently was not involved by the tumor. The lamina papyracea, which was in close contact with the tumor, was resected, with care not to injure the anterior and posterior ethmoid arteries. Superiorly, the

dissection started at the agger nasi level and in front of the lamina cribrosa and extended medially to include the mucosa covering the upper third of the septum. The middle turbinate was resected, and the lesion was peeled off the roof of the ethmoid sinus and the lamina cribrosa. During these maneuvers, a cerebrospinal fluid leak coming from a 5-mm bony dehiscence in the vertical lamella of the cribriform plate was observed.

The dissection was carried further posteriorly to include the superior turbinate and to reach the anterior wall of the sphenoid, which was full of inspissated mucus but was not involved by the tumor. The residual lesion was transorally removed en bloc with the middle and superior turbinates, and multiple biopsy specimens were taken at the resection margins. Because the biopsy specimen obtained from the septum showed tumoral tissue, a large area of the bony and cartilaginous parts of the septum was resected. A composite graft harvested in the left nasal fossa from the residual anterior part of the septum and made of a small cartilaginous fragment with the overlying mucosa was fixed in place with fibrin glue to seal the cerebrospinal fluid leak. The nasal cavity was left packed with Lyofoam (Seton Healthcare Group, Oldham, England) for 4 days.

The postoperative course was uneventful, and the patient was discharged from the hospital 6 days after the operation. She underwent follow-up visits every 3 months and was free of disease at the last endoscopic (Fig 2) and CT evaluations (Fig 3), 36 months after surgery.

Microscopically, the tumor consisted of fascicles

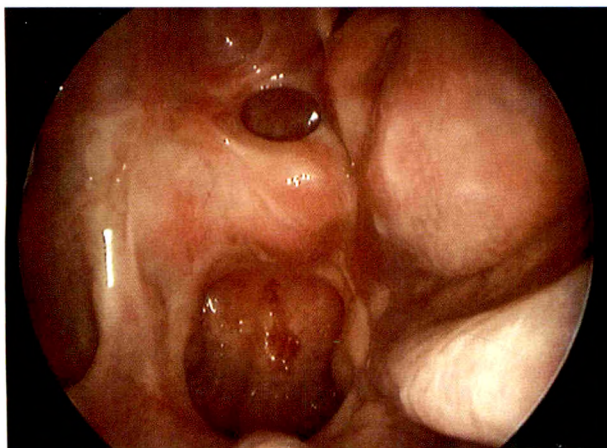


Fig 2. Endoscopic view (0° rigid fiberscope) of nasal cavities 3 years after surgery. Wide communication of right maxillary sinus with nasal fossa, as well as patency of sphenoidotomy, is clearly visible. No signs of recurrent tumor are evident.



Fig 3. Follow-up computed tomography scan in coronal plane 3 years after surgery demonstrates reossification of right fovea ethmoidalis (arrowhead) and thickening of right lamina papyracea.

of closely packed spindle cells, with buckled nuclei and indistinct cytoplasmic borders. Focally rounded or strap-shaped rhabdomyoblasts with large, eosinophilic cytoplasm were present (Fig 4A). Focal glandular structures were also found. The mitotic index was low (1 mitosis per 10 high-power fields), and there was no necrosis. A variable percentage of tumor cells were positive for S-100 protein; the rhabdomyoblasts showed an intense reactivity for desmin (Fig 4B) and muscle-specific actin.

DISCUSSION

The combination of a malignant peripheral nerve sheath tumor with rhabdomyosarcomatous elements is termed MTT.⁵ The tumor is a very rare clinicopathologic entity, with about 90 cases so far reported.⁶⁻¹² According to the results of a world literature review made by Woodruff and Perino,⁶ the tumor predominantly affects young patients, with a mean age of 34 years, and is associated in 57% of cases with NF-1. Patients with NF-1 appear to be slightly younger (31 years) than patients without NF-1 (37 years).⁶ The tumor has no peculiar site distribution and almost equally occurs in the limbs, head and neck, and trunk.

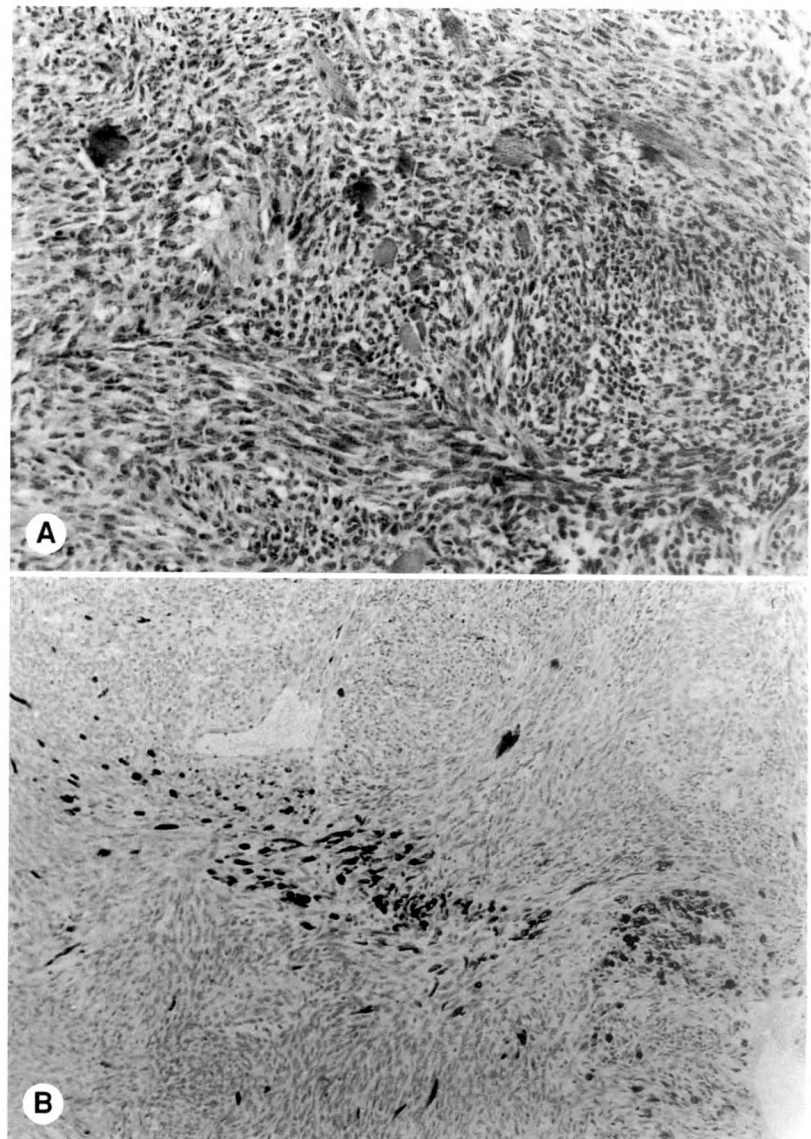
The histogenesis of MTT is controversial. On the basis of Locatelli's work,³ Masson and Martin¹³ postulated that the endoneural cells in the tumor could induce the formation of muscle in a manner similar to that seen in supernumerary limb regeneration in the Triton salamander. Further investigations, however, showed that aneurogenic forelimbs of Tritons may also regenerate and that limb and muscle regeneration in Tritons is independent of motor nerve innervation.^{14,15} A second and more widely accepted hypothesis proposed by the same authors suggested that neoplastic Schwann cells directly transform into striated muscle elements.^{14,15}

A teratoid origin^{16,17} is less likely, because endodermal elements are absent, and all components of the tumor are obviously atypical. Finally, the theory proposed by Holimon and Rosenblum¹⁸ and Naka et al,¹⁹ which unifies the embryogenesis and histogenesis of the different mesenchymal elements present in MTT, is based on the concept of "ectomesenchyme": the migratory cells of the neural crest show divergent differentiation into mesenchyme (leptomeninges, bone, cartilage, and muscle of head and face) and into neuroectodermal structures (melanocytes, ganglion cells, and Schwann cells) during embryonic life. The cells, although widely present throughout the body, are believed to retain their capacity for mesenchymal differentiation in adult life. The multiple differentiation capacity of neural crest cells is further illustrated by reports of tumors composed of mixed neural crest derivatives, as well as the occurrence of neurosarcomatous transformation in a melanoma.^{20,21}

Histopathologic criteria for MTT diagnosis, as established by Woodruff et al,² require that the tumor 1) arise along the course of a peripheral nerve, or in a patient with NF-1; 2) largely show the growth characteristics of a Schwann cell tumor; and 3) contain bona fide neoplastic rhabdomyoblasts. Daimaru et al²² also regarded as MTTs tumors that arise in patients without NF-1 that are microscopically compatible with malignant schwannoma with focal rhabdomyoblasts, as well as tumors that occur within a nerve or in patients with NF-1 that show a predominantly rhabdomyoblastic differentiation with focal Schwann cell elements.

Head and neck sites were involved in less than one third of the MTTs reported in the literature: 8 patients had the tumor localized in the neck,^{1,2,23-26} 3 in the cerebellopontine angle,^{11,27,28} 2 in the soft tissues of the face,^{21,29} 2 in the parotid gland,^{10,23} 2 in the thyroid gland,^{30,31} and 1 each in the infratemporal fossa,¹² oral cavity,³² and temporal fossa.³³ Involvement of the sinonasal tract by MTT (Table 2³⁴⁻³⁶) was first documented by Shajrawi et al³⁴ in a 75-year-old man who was treated with a debulking procedure and complementary radiotherapy. The patient was free of disease 6 months after a single recurrence 3 years after the first treatment. In a report by Bhatt et al,³⁵ MTT occurred in a 66-year-old woman and was grossly excised through an extended external ethmoidectomy approach. The patient was alive with disease 27 months after surgery. The remaining 5 cases were described by Heffner and Gnepp³⁶ in 1992; they occurred in 4 men and 1 woman, ages 43 to 64 years. The initial treatment consisted of a partial removal of the tumor in 2 cases: 1 patient died of the disease 26 months after surgery, and the other was alive with

Fig 4. Histologic analysis. A) Densely intersecting spindle cells and myoid cells (H & E, original $\times 40$). B) Rhabdomyoblasts (strongly desmin-positive) are clustered in focal areas of tumor (desmin stain, original $\times 20$).



disease 27 months after treatment. The other 3 patients underwent a more radical surgical approach, but 2 of them experienced a locoregional recurrence that was controlled by rescue surgery. The 3 patients were free of disease 8, 21, and 22 years after surgery. It is noteworthy that no case involving the sinonasal tract, including ours, was associated with NF-1 or displayed histologic features of high aggressiveness.

The endoscopic and radiologic appearance of MTT did not differ significantly from that of other malignancies of the sinonasal tract. In the present case, only the finding on the CT scan of a marked and irregular bony thickening of the ethmoid septa and middle turbinate was peculiar, and it could suggest a diagnosis of osteogenic sarcoma. As with any other mass involving the nose and paranasal sinus, MRI is indeed the radiologic examination of choice, because it has the advantage over CT of allowing a multipla-

nar evaluation of the lesion, a better differentiation of neoplastic tissue from inflammatory changes, and a superior delineation of the relationship between the mass and some important adjacent structures (ie, orbit, dura, internal carotid artery).³⁷

The prognosis of MTT has been analyzed by several authors,^{6,9} who found that the tumor is more aggressive than malignant peripheral nerve sheath tumors, with 5-year crude and specific survival rates of 11% and 26%, respectively. Yakulis et al⁹ also looked at the impact on the survival rate of different variables such as location of the tumor, age, sex, and association with NF-1 by means of a Cox regression analysis. Lesions that occurred in the upper extremities, lower extremities, and head and neck had a better outcome than those that arose in the retroperitoneum, buttocks, or trunk. The observation is supported by a recent study of Victoria et al,¹² who confined their review to head and neck patients and found

TABLE 2. MALIGNANT TRITON TUMOR OF SINONASAL TRACT: REVIEW OF LITERATURE

Study	Age (y)	Sex	NF-1	Site	Symptoms and Signs	Treatment	Re-treatment	Outcome
Shajrawi et al ³⁴ (1989)	75	M	No	Left maxillary, ethmoid, and sphenoid sinuses	Left epistaxis	Debulking and RT	Removal of local recurrence through Caldwell-Luc procedure, 36 mo	Alive without evidence of disease, 6 mo after re-treatment
Bhatt et al ³⁵ (1991)	66	F	No	Left nasal cavity, ethmoid sinus, and orbit	Left nasal obstruction, epistaxis	Excision through extended external ethmoidectomy		Alive without symptoms but with CT evidence of tumor regrowth in posterior ethmoid, 27 mo
Heffner and Gnepp ³⁶ (1992)	64	M	No	Left nasal cavity		Incomplete excision		Dead of local recurrence and pulmonary metastases, 26 mo
	58	M	No	Nasal cavity	Nasal obstruction	Surgery and RT		Alive without evidence of disease, 48 mo
	56	F	No	Left nasal cavity	Nasal obstruction	Local excision	Removal of local recurrences through fronto-ethmoidectomy, 11 and 15 y	Alive without evidence of disease, 7 y after last treatment
	59	M	No	Right nasal cavity	Epistaxis	Transpalatal excision and RT		Alive without evidence of disease, 7 y
	43	M	No	Right nasal cavity	Nasal obstruction	Not known	Recurrence (no information on treatment), 15 y	Alive without evidence of disease, 7 y after recurrence
Present case	81	F	No	Right nasal cavity, ethmoid sinus	Nasal obstruction	Endoscopic excision		Alive without evidence of disease, 36 mo

NF-1 — neurofibromatosis type 1, RT — radiotherapy, CT — computed tomography.

a 26% overall 5-year survival rate. Even though most of the authors emphasize the negative impact of the association with NF-1 on MTT prognosis,^{6,24} the concept was not confirmed by the statistical analysis made by Yakulis et al.⁹ The rarity of the disease in the sinonasal tract prevents us from drawing meaningful conclusions on the prognosis. However, it is noteworthy that 6 of the 8 documented patients (Table 2) were alive without evidence of disease even after a long follow-up.

It is always difficult to speculate on treatment guidelines when dealing with a rare disease. However, as with any other sarcoma, resection of the tumor with a wide margin followed by radiotherapy is generally recommended, and the role of chemotherapy has not yet been clearly defined.¹² In the sinonasal tract, treatment planning should be made according to tumor extent, involvement of vital structures, histologic aggressiveness of the lesion, and patient profile. In the case herein reported, the pres-

ence of an erosion of the anterior skull base and the large volume of the tumor suggested a craniofacial resection as the first-option treatment. However, the low mitotic index of the tumor, the age of the patient, and her desire for a less invasive procedure, together with our experience in the endoscopic treatment of selected benign and low-grade malignant tumors of the sinonasal tract and nasopharynx, prompted us to consider endoscopic removal as a second choice. Originally described in the late 1970s for the treatment of inflammatory diseases of the sinonasal tract,³⁸ endonasal surgery with the help of rigid endoscopes or a microscope has expanded its indications to include the treatment of inverted papilloma,³⁹⁻⁴⁴ juvenile angiofibroma,⁴⁵⁻⁴⁷ and selected malignant lesions.⁴⁷ In our experience, endoscopic surgery enables en bloc removal of small and medium-sized lesions. In larger tumors, particularly if malignant, debulking is first needed to expose the area in which the tumor arises and to judge the degree of involvement of some critical areas, such as the lamina

papyracea and the skull base, which may necessitate conversion to an external procedure. Magnification and the close view of structures offered by rigid endoscopes help to differentiate normal and diseased tissues, as well as to identify the relevant surgical landmarks, even those distorted by the pathological process. As with any surgical procedure performed for a tumor, the radicality of the resection should be evaluated by multiple frozen sections. Furthermore, frequent endoscopic and radiologic follow-up evaluations are mandatory for early detection and consequent treatment of a recurrent tumor.

In conclusion, we have reported the eighth case of

MTT of the sinonasal tract, a rare disease that otolaryngologists should be aware of and that must be included in the differential diagnosis of malignant lesions involving the sinonasal tract. Clinical and radiologic pretherapeutic evaluation is directed not only at defining the extent of the disease, but also at identifying a possible association with NF-1. Although, in the present case, endoscopic surgery enabled a good oncological result with minimal morbidity and a short hospitalization, more extensive experience based on a large number of patients with adequate follow-up is certainly required to properly define the possibilities and limitations of endoscopic surgery in the treatment of neoplastic lesions of the sinonasal tract.

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SOFTWARE REVIEW

VOICE NOTES: THE COMPREHENSIVE GUIDE TO THE CLINICAL DIAGNOSIS AND TREATMENT OF LARYNGEAL PATHOLOGY

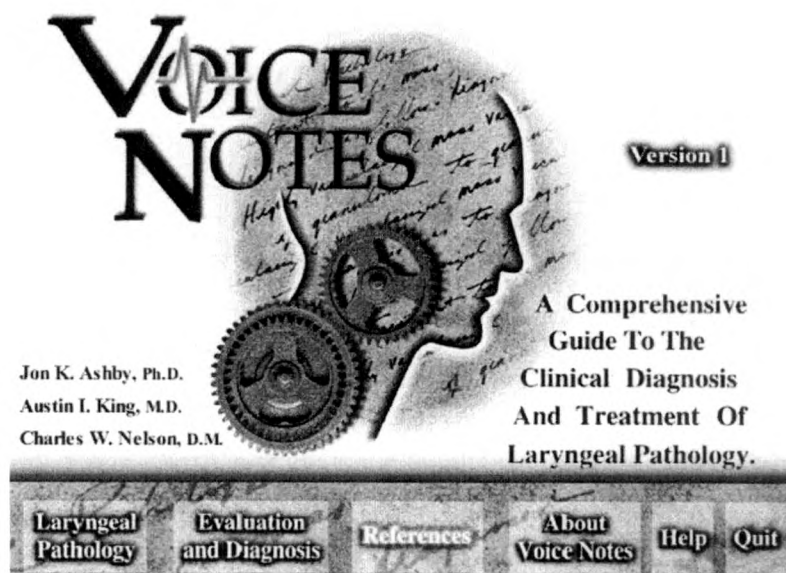
Company: Allyn & Bacon, 160 Gould St, Needham Heights, MA 02494.

Hardware requirements: A Macintosh system requires a power PC, 24 MB of RAM, a hard drive with 10 MB free, CD-ROM drive (4X), 16-bit sound card, color monitor, 24 bit color, 640 × 480 pixel display. The PC requirements are Windows 95/98, Windows NT 4.0 or later, Pentium 100 MHz, 16 MB of RAM, hard drive with 10 MB free, CD-ROM drive (4X), 16-bit sound card, color monitor, 24 bit color, 640 × 480 pixel display.

The Voice Notes software system is a compact system that categorizes laryngeal disorders into mass lesion, movement, and functional disorders. Each specific type of disease is introduced with a pictorial or auditory presentation, a written synopsis of the disorder, and specific voice notes about the patient and disorder introduced. Extending the QuickTime video and adding samples of connected speech would prove valuable and enhance the overall usefulness of this tool. Many of the auditory and pictorial presentations are of poor quality. Navigation through the system is easy and understandable to the new user. The system can be accessed through the use of a navigational hierarchy (table of contents), an outline, and a page-turning feature (see Figure).

Functional disorders are categorized as singing disorders and speech disorders. The singing disorders discussed include arytenoid arch, hard attack, open pharynx, and rising larynx. The speech disorders de-

finied include ventricular fold approximation, hyperfunction, nonorganic disorders, and mutational falsetto. Mass lesions are categorized as mucosal covering disorders, submucosal disorders, and supporting structure conditions. The mucosal covering disorders discussed are as follows: cancer, granuloma, precancerous conditions, infectious conditions, inflammatory conditions, nodules, and papilloma. The submucosal disorders include cysts, hemorrhage, polyps, sulcus vocalis, and varicosity. The supportive structure disorders include systemic conditions, traumatic conditions, and laryngeal web. The movement disorders are further defined as laryngeal innervation disorders, neurologic disorders, and progressive neuromuscular disorders. The laryngeal innervation disorders include recurrent laryngeal nerve paralysis and superior laryngeal nerve paralysis. The neurologic disorders are subcategorized into spastic dysphonia and paradoxical vocal fold motion condition and tremor. The progressive neuromuscular diseases include



Parkinson's disease, amyotrophic lateral sclerosis, and myasthenia gravis. All information provided in the laryngeal pathology section is concise, easily accessed, and correct.

The Voice Notes software system also includes an evaluation and diagnosis section. This section presents a "clinical voice lab," which has an introduction, a patient history, sample forms, and a voice history. An instrumental analysis subsection includes acoustic analysis and physiological measurement. This subsection outlines such topics as computerized analysis, instrumentation, measurement techniques, sterilization, and anesthesia. A visual analysis section discusses the use of video recordings. It also provides an introduction to fiberoptic examination. This section includes a discussion of the advantages, the procedure, rating systems, and anesthesia. The use of rigid scopes, the use of mirrors for indirect laryngoscopy, and stroboscopy are outlined. As a whole, the diagnosis and evaluation section appears introductory in nature. The sample forms provided are simple and concise. The computerized analysis

section is excellent and covers voice irregularity, subharmonics, measurement of voice breaks, measurement of tremor, measurement of inharmonics (noise), short- and long-term frequency perturbation, short- and long-term amplitude perturbation, and fundamental frequency information.

In summary, Voice Notes is an easy-to-access, compact guide to voice disorders. Although the information provided is useful and correct, it would prove most useful to medical students and speech pathologists as a part of "introductory" course work. The pictorial and auditory quality needs improvement. The Laryngeal Pathology section would benefit if a "connected speech" sample were added for each disorder. In the Diagnosis and Evaluation section, the computerized analysis section is excellent and easily understood.

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MULTIDISCIPLINARY AIRWAY STENT TEAM: A COMPREHENSIVE APPROACH AND PROTOCOL FOR TRACHEOBRONCHIAL STENT TREATMENT

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Tracheobronchial stents are being used with increasing frequency to treat major airway obstruction from both malignant and benign processes. Traditionally, stents have been placed via rigid bronchoscopy, flexible bronchoscopy, or fluoroscopy by members of various individual disciplines. We describe a novel multidisciplinary airway stent team (MAST) protocol for tracheobronchial stent placement and endoscopic management of major airway obstruction. A patient with symptoms of airway obstruction is generally first evaluated with a computed tomography scan and a videotaped flexible bronchoscopy. These studies are reviewed by the team otolaryngologist, pulmonologist, and interventional radiologist. A treatment plan, including the type and location of stents and the need for adjuvant therapies, is formulated. Stent placement is performed in the operating room under general anesthesia. Rigid bronchoscopy, with flexible bronchoscopy and fluoroscopy as needed, allows precise stent placement and the best use of various therapeutic methods. The MAST protocol combines the skills, knowledge, and unique therapeutic options of specialists from otolaryngology, pulmonology, and interventional radiology. This approach allows optimal stent placement and the use of other endobronchial therapies, including laser ablation, balloon dilation, photodynamic therapy, cryotherapy, and brachytherapy. A protocol with representative case reports is presented, along with a review and comparison of several of our most commonly used stents. Otolaryngologists who practice bronchoesophagoscopy, by virtue of their operative skill and knowledge of airway management, are well equipped to become leaders of MASTs and are encouraged to initiate MASTs at their institutions.

KEY WORDS — airway obstruction, bronchoscopy, stent.

INTRODUCTION

Obstructive tracheobronchial lesions may be life-threatening. In the last decade, airway stents have become a valuable adjunct to relieving such severe obstruction.¹⁻⁴ Stents may be used to treat benign airway obstruction,⁵⁻⁹ but they are used most commonly as palliative therapy in patients with major airway obstruction secondary to unresectable malignancy.¹⁰⁻¹⁷ Indications for stenting include 1) extrinsic malignant obstruction when curative options and other palliative efforts have been exhausted, 2) symptomatic benign strictures and stenoses where excision, laser resection, and dilation have failed, 3) severe tracheobronchomalacia, and 4) tracheoesophageal or bronchoesophageal fistulae due to malignancy.¹⁸

Previously, stent placement was performed separately by pulmonologists, interventional radiologists, thoracic surgeons, or otolaryngologists. This article describes a novel approach involving a multidisciplinary airway stent team (MAST) that evaluates the patient, determines the best therapeutic option, and places stents or uses other therapeutic methods as

needed. The primary members of the team are an otolaryngologist, a pulmonologist, and an interventional radiologist. A MAST approach ensures that each patient receives the most appropriate therapy performed in the best possible manner.

CASE REPORTS

Our MAST routinely performs 1 to 2 stent placements per month for a variety of disorders. Multiple types of stents may be used (Fig 1). We provide here representative case reports to illustrate the MAST protocol.

Case 1. A 71-year-old man with a history of squamous cell carcinoma of the esophagus was transferred to our institution, requiring 100% oxygen by face-mask. Esophageal carcinoma with compression and invasion of the trachea had been diagnosed by endoscopy 7 months before admission. The extensive tumor was unresectable, and chemotherapy and external beam radiotherapy had been given, with minimal relief of his dysphagia and dyspnea. A computed tomography (CT) scan of the neck and chest revealed

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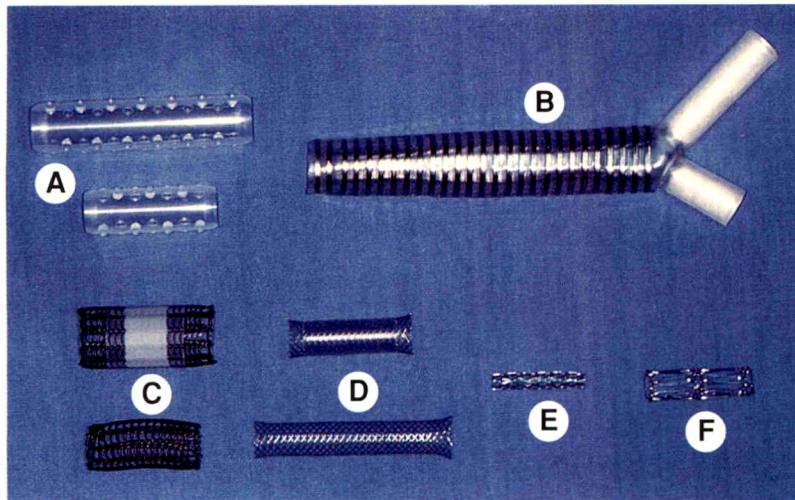


Fig 1. Common endoscopic airway stents include A) silicone studded Dumon stent, B) Y-shaped Dynamic stent composed of silicone with stainless steel supporting tracheal arches, C) nitinol Ultraflex mesh stent (covered and uncovered), D) Wallstent super alloy wire mesh stent (covered and uncovered), E) Palmaz balloon-expanded stainless steel stent, and F) Gianturco zig-zag metal stent.

a large mediastinal mass to the right of the esophagus, with compression and invasion of the trachea posterolaterally, causing a 90% obstruction of the airway. The obstruction extended from 3 cm below the vocal cords to 2 cm above the carina. The patient was taken urgently to the operating room for evaluation and stent placement.

Under general anesthesia, a ventilating laryngotracheoscope (Karl Storz, Culver City, Calif) was placed proximal to the lesion. A slim, flexible bronchoscope was then placed through the laryngotracheoscope to permit examination of the extent of the obstruction. No airway obstruction was noted distal to the trachea. A Nd:YAG laser was used to debulk the intraluminal tracheal mass. A tracheal Wallstent (Schneider, Minneapolis, Minn) was introduced and deployed with fluoroscopic and bronchoscopic guidance. Angioplasty balloon catheters were used successfully to fully dilate the stent. The patient had postoperative oxygen saturations of 96% on room air and was able to breathe comfortably. He was discharged 2 days after the operation. The patient survived more than 7 months after initial stent placement without the need for further operative intervention (Fig 2).

Case 2. A 70-year-old woman presented with increasing dyspnea on exertion and decreasing functional status. She had a 50-pack-year tobacco history. A CT scan revealed a large paratracheal mass near the carina, partially obstructing the trachea and totally obstructing the right main stem bronchus. Bronchoscopic biopsy revealed a poorly differentiated carcinoma. She received a course of external beam radiotherapy, declined chemotherapy, and developed progressive dyspnea. A Nd:YAG laser ablation and debulking of the tumor opened the right main stem bronchus. A Dynamic stent was inserted through a laryngotracheoscope with the aid of a special introducer forceps and fluoroscopy. Ten months later,

her airway remains patent (Fig 3).

Case 3. A 5-month-old boy presented with total anomalous pulmonary venous return necessitating 2 separate open heart procedures. Recurrent left lung pneumonias, wheezing, and a requirement for supplemental oxygen prompted chest CT and bronchoscopy. Contrast-enhanced scans were done with an electron beam CT scanner set for 100-ms scans. A CT scan revealed significant extrinsic left main stem compression, anteriorly by the right pulmonary artery, and posteriorly by the descending aorta (Fig 4A). Bronchoscopic evaluation revealed severe left main stem bronchomalacia (Fig 4B). Under rigid bronchoscopy, a Palmaz stent (Johnson and Johnson Interventional Systems, Warren, NJ) was positioned with telescopic and fluoroscopic guidance (Fig 4C). The stent was balloon-expanded to a diameter of 4 mm (the same diameter as the normal right main stem bronchus). The child was discharged within 24 hours with a normal pulmonary examination and no supplemental oxygen. Scans performed 2 weeks later with high-resolution electron beam CT revealed a patent left main stem bronchus with insignificant indentation of the pulmonary artery and no compression of the aorta (Fig 4D).

The child's growth necessitated another electron beam CT scan 3 months later. High-resolution scans showed recurrent narrowing of the left main stem bronchus proximal to the end of the stent, consistent with bronchial lengthening and recurrent bronchomalacia. A second telescoping Palmaz stent was placed. The patient will need bronchoscopic evaluation with possible balloon dilation every 6 to 12 months for at least 5 years.

Case 4. A 63-year-old woman with insulin-dependent diabetes mellitus and dementia presented with stridor and dyspnea on exertion a month after 3 weeks of intubation for a diabetic ketoacidotic coma at an-

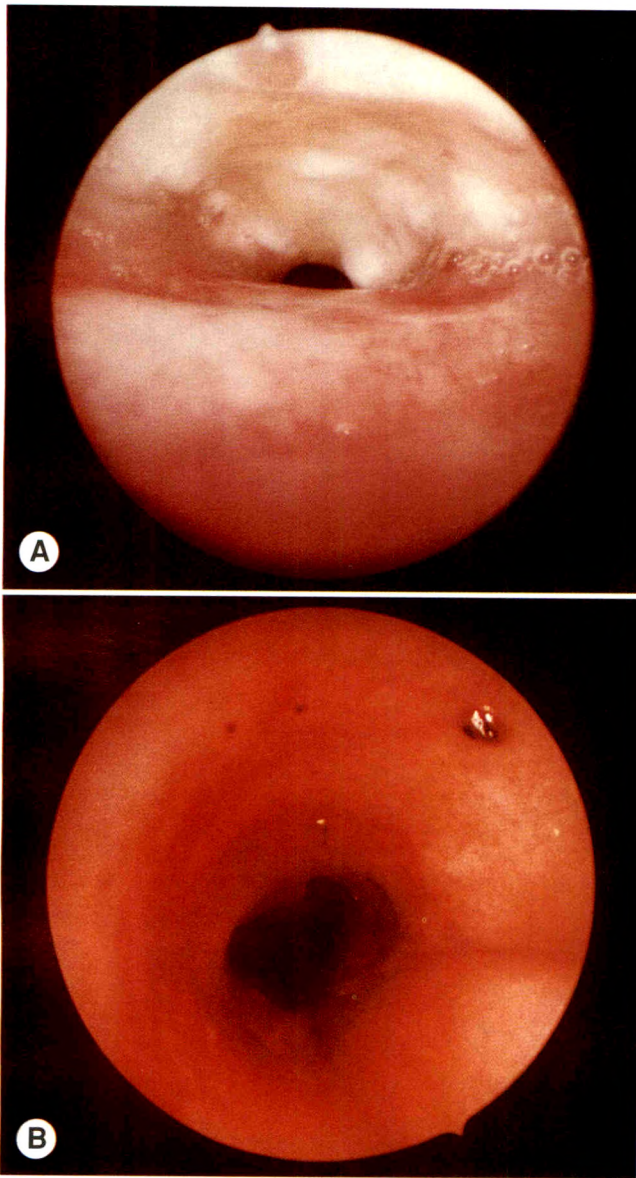
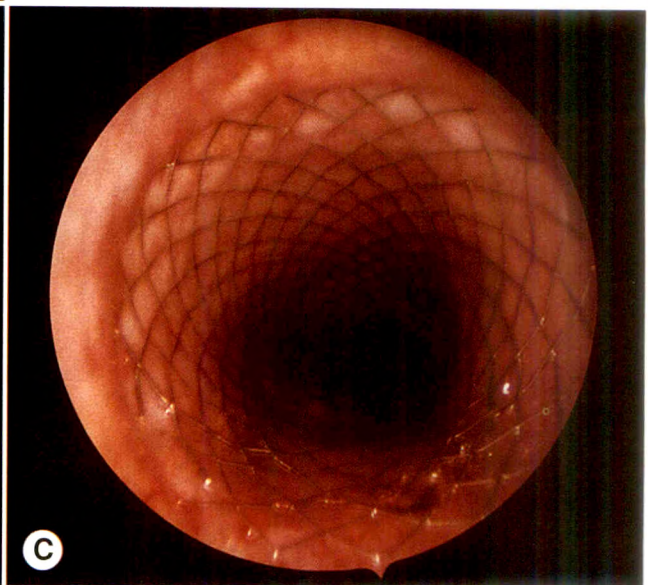
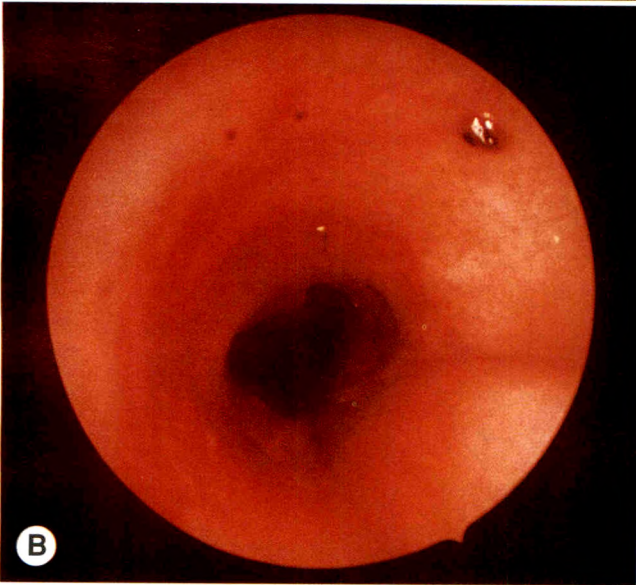


Fig 2. (Case 1) A) Esophageal cancer eroding into trachea, causing near-total obstruction. B) Tracheal airway after Nd:YAG laser debulking. C) Improved tracheal airway after Wallstent placement.



other institution. Flexible bronchoscopy and a CT scan of the neck and thorax revealed stenosis of the trachea at the level of the thoracic inlet, consistent with endotracheal tube cuff injury. The stenosis was 2 cm long, and the residual lumen was 2 mm in diameter. A low tracheotomy was not favored because of the patient's dementia and poor wound healing history. A ventilating laryngotracheoscope was placed under general anesthesia, and a KTP laser was used to vaporize the stricture with radial cuts. A Dumon silicone stent (Hood Laboratories, Pembroke, Mass) was then placed (Fig 5). The patient was soon discharged with resolution of symptoms.

Three weeks later, the patient noted recurrence of stridor. Flexible bronchoscopy revealed distal migration of the stent, with a flap of granulation tissue obstructing the proximal end of the stent. Under general anesthesia, the stent was gently grasped with opti-

cal forceps and repositioned. The patient was discharged without difficulty after overnight observation.

Five months later, the stent was removed under a planned general anesthesia. Within 24 hours, the stridor recurred, with notable circumferential edema and granulation. A nickel-titanium Ultraflex stent (Boston Scientific, Natick, Mass) was positioned, with resolution of stridor and airway distress. Follow-up bronchoscopic examinations revealed a widely patent trachea and a mucosalized stent without granulation tissue. The patient has no respiratory symptoms, 1 year after Ultraflex stent placement.

PROTOCOL

In our MAST protocol, the patient is commonly first evaluated by the pulmonologist. If the history and physical examination indicate that an obstruc-

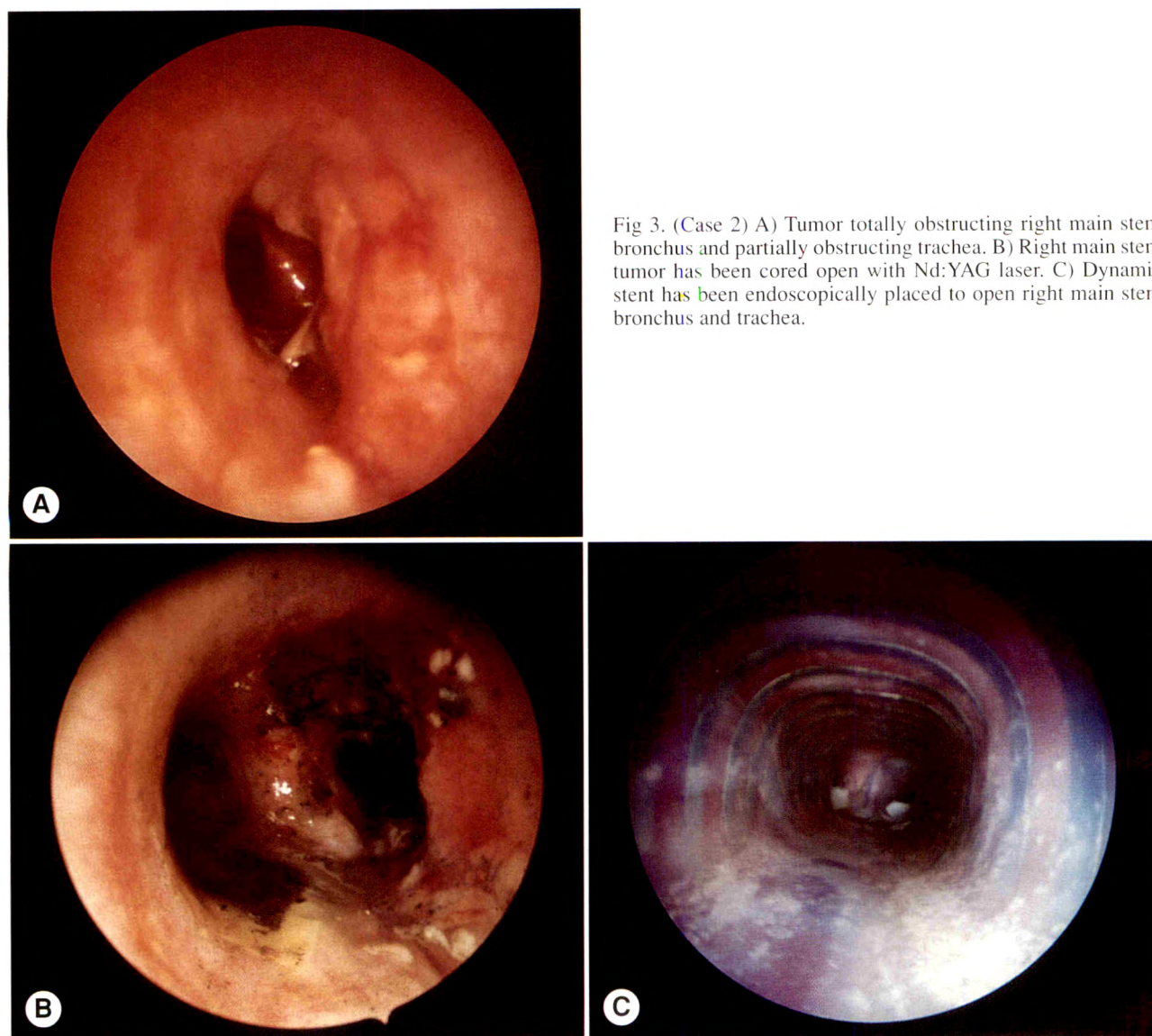


Fig 3. (Case 2) A) Tumor totally obstructing right main stem bronchus and partially obstructing trachea. B) Right main stem tumor has been cored open with Nd:YAG laser. C) Dynamic stent has been endoscopically placed to open right main stem bronchus and trachea.

tive lesion is likely, a chest radiograph, pulmonary function tests, and a videotaped flexible bronchoscopy are performed and reviewed with the otolaryngologist and interventional radiologist. A CT scan of the neck and thorax is obtained to determine the full extent of the obstruction and its spatial relationship to significant vessels and viscera. Electron beam CT is preferred, because it can scan faster, with higher resolution.¹⁹ The combination of CT scan and flexible bronchoscopy provides an optimal preoperative indication of stent diameter and length. The stent diameter is calculated by carefully measuring the diameter of the adjacent uninvolved airway on the CT scan. An inappropriately small-diameter stent may migrate. An inappropriately large-diameter stent may have an irregular shape and not fully deploy. The stent length is determined by CT scan measurements and is confirmed by direct bronchoscopic measurement. The stent length should extend at least 1 cm beyond

the lesion on either side. A short stent may migrate. A long stent may unnecessarily disrupt mucociliary clearance, with extensive stenting of the normal trachea or bronchus. A treatment plan is devised that includes the type, size, and location of the stent(s) to be placed, as well as adjuvant treatment methods such as laser resection, balloon dilation, photodynamic therapy, and brachytherapy.²⁰ If, upon initial presentation, the airway is unstable and needs emergent intervention, the usual preoperative protocol is bypassed and the patient goes immediately to the operating room for airway control with rigid bronchoscopy and possible stenting.

All procedures are performed in the operating room under general anesthesia, with the thoracic surgeon available for consultation in case an untoward mediastinal complication should arise. Alternatively, simple stent placement may be performed in a fully

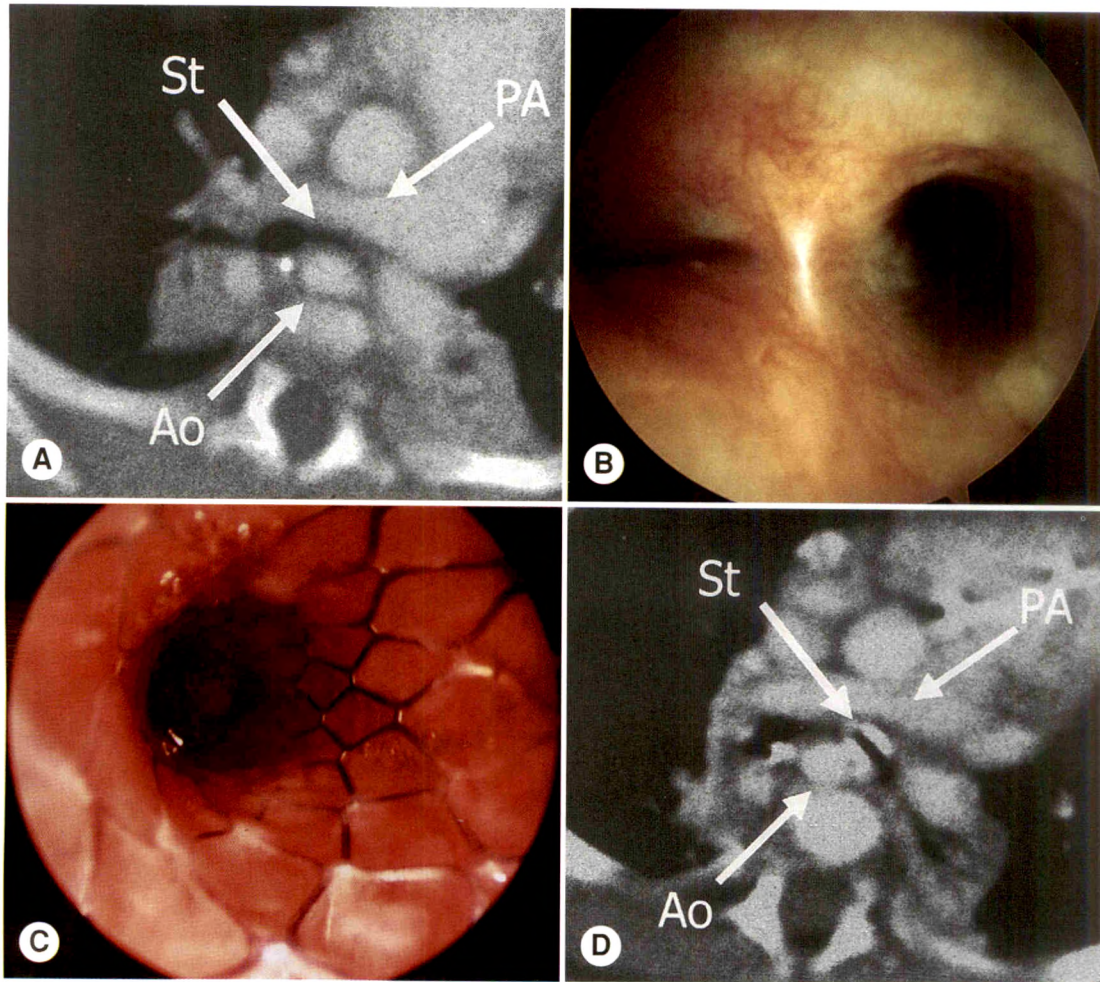


Fig 4. (Case 3) A) Initial contrast-enhanced scan using electron beam computed tomography shows compression of left main stem bronchus (St) between pulmonary artery (PA) and aorta (Ao). B) Severe left main stem bronchomalacia before operation. C) Patent left main stem airway with Palmaz stent. D) Electron beam computed tomography performed after stent placement reveals patent left main stem bronchus (St), insignificant indentation of pulmonary artery (PA), and patent aorta (Ao).

equipped interventional radiology suite set up similarly to the operating room. The presence of an experienced anesthesiologist comfortable with rapid sequence induction, "sharing" the airway, and various bronchoscopic inhalation techniques is critical. A ventilating laryngotracheoscope (Fig 6) is placed under telescopic guidance, with the tip proximal to the lesion. The laryngotracheoscope allows for simultaneous ventilation with a protected airway and passage of telescopes, stents, and instruments. The flexible bronchoscope is placed through the laryngotracheoscope to visualize and treat more distal lesions. Either Nd:YAG or KTP laser treatment and/or mechanical debulking with optical forceps may be used to open the airway before stent placement, if the obstruction has a significant intraluminal component. Mechanical debulking permits more rapid management of obstructive malignant masses; however, the risk of increased hemorrhage must be considered. Alternatively, balloon dilation may be used in con-

junction with laser therapy or mechanical debulking. A combination of fluoroscopy and direct endoscopic visualization allows for more precise stent placement. Serial postoperative bronchoscopic stent examinations are performed under either local or general anesthesia, depending on the patient's age and the severity of disease.

DISCUSSION

The use of stents to treat tracheobronchial obstruction is increasingly common. Yet, in spite of the excellent qualifications of otolaryngologists to treat such lesions, there is a relative paucity of reports on this topic in the otolaryngology literature.^{3,15,21-23} Endoluminal tracheobronchial stents represent a significant advancement in the treatment of major airway obstruction and may be used in conjunction with other endoscopic methods such as mechanical dilation,²⁴ laser resection,^{1,11} brachytherapy,²⁵ photodynamic therapy,^{1,10} and cryotherapy.²⁶

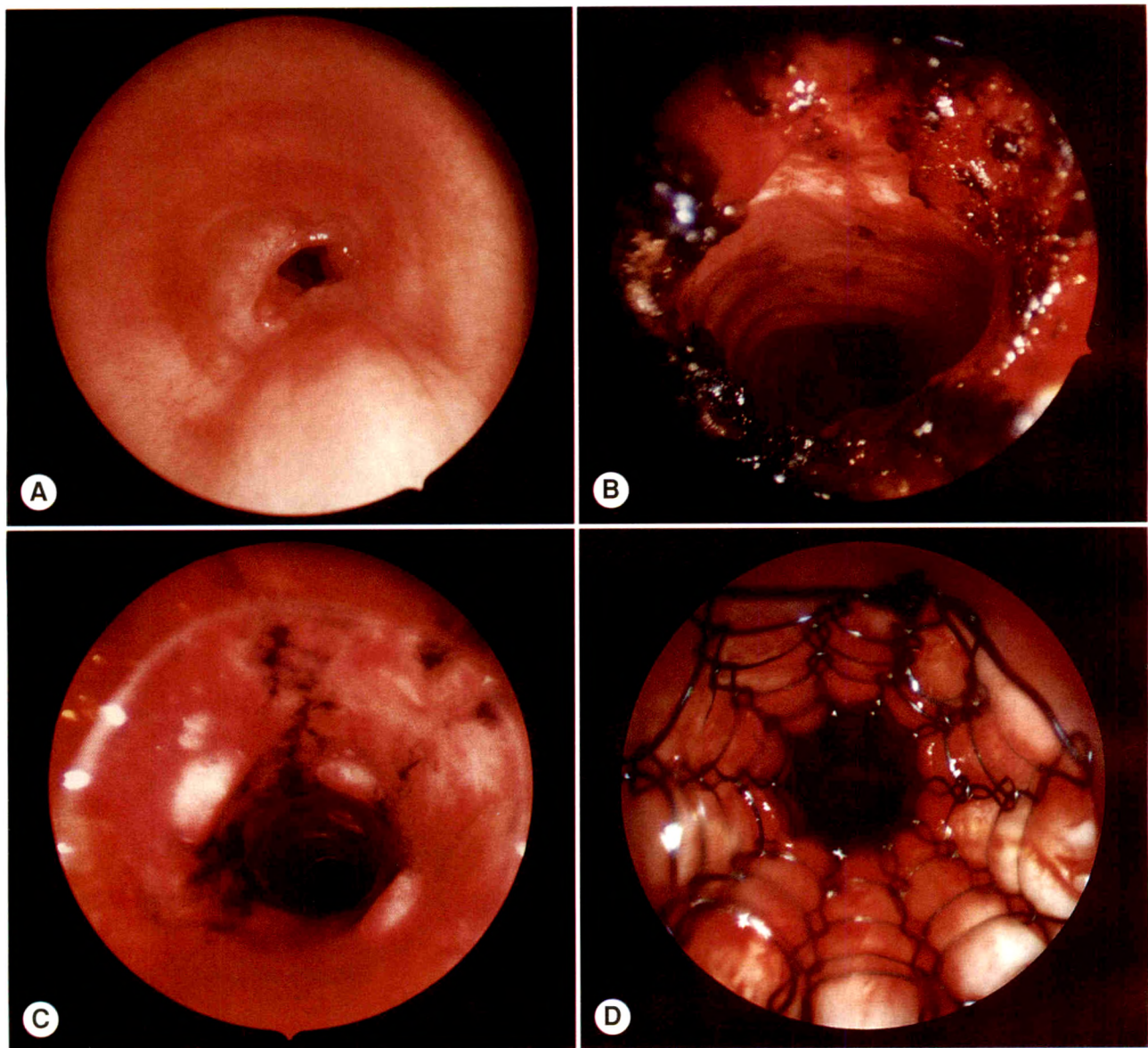


Fig 5. (Case 4) A) Tight tracheal stenosis caused by endotracheal tube cuff injury. B) Airway opened with potassium titanyl phosphate laser. C) Endoscopic view through temporary plastic Dumon stent. Note tracheal patency, stent posts, and laser burns from radial incisions. D) Tracheal stenosis that recurred after Dumon stent removal required permanent use of Ultraflex stent, seen here.

Balloon dilation is commonly used before and after stent placement. Angioplasty balloons are superior to Fogarty embolectomy catheters or Foley catheters for dilation of major airway obstructions, because of their uniform application of high pressure to a specified length and diameter. Cases 1 and 3 demonstrate the usefulness of balloon dilation with angioplasty catheters.

The laser most commonly used for endoscopic treatment of tracheobronchial lesions is the Nd:YAG.^{1,17,27} The main advantage of the Nd:YAG laser over the CO₂ laser is delivery via a flexible fiber. This allows improved control and ability to direct the beam precisely at the target tissue, as well as al-

lowing treatment of more distal lesions. The advantages of the pre-stent use of the Nd:YAG laser are demonstrated in cases 1 and 2. Additionally, the Nd:YAG laser provides improved photocoagulation and deeper thermal tissue necrosis for better control of malignant cases.²⁷ For benign intraluminal strictures, the KTP laser is preferred because of its tissue vaporization effect with less penetration into deep tissues. Laser resection provides quick, effective opening of the airway in cases in which tumor or fibrosis causes symptomatic intraluminal obstruction.¹¹ After palliative laser resection of malignant lesions, stent placement and/or brachytherapy are commonly used in an effort to prolong airway patency.

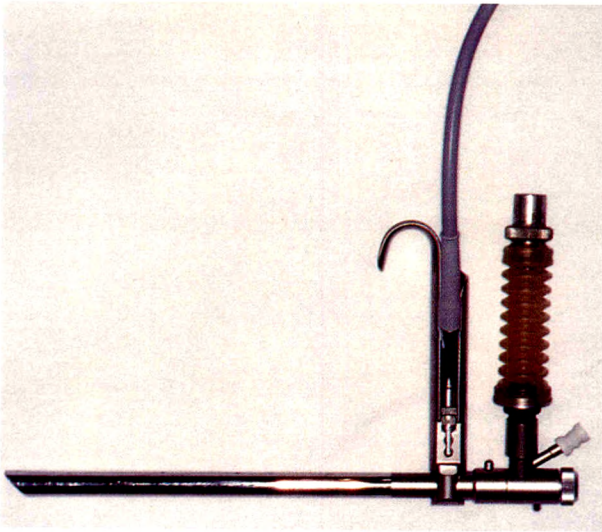


Fig 6. Karl Storz ventilating laryngotracheoscope. This suspendable instrument allows proximal ventilation, airway control, visualization, stenting, use of laser, and dilation.

Less often, we combine stenting with photodynamic therapy, cryotherapy, and brachytherapy. Photodynamic therapy is best suited for treatment of early, superficial carcinomas with curative intent and is less appropriate for palliation of larger, obstructing lesions.²⁸ Cryotherapy may be used instead of lasers to remove tumor within a stent, thus avoiding potential laser fires. Brachytherapy provides an option for palliation of malignant airway obstruction in patients who have had maximal-dose external beam radiotherapy. Unfortunately, high-dose rate brachytherapy is associated with fatal hemorrhage in more than 20% of the patients treated.²⁵ When brachytherapy is used after nonexpandable stent placement, the risk of stent migration may increase because of tumor shrinkage.

The MAST protocol for the endoscopic management of tracheobronchial obstruction optimizes patient care. This model uses rigid bronchoscopy in combination with flexible bronchoscopy and radiographic techniques. Team members include pulmonologists, interventional radiologists, and otolaryngologists. Additionally, a thoracic surgeon is on call to surgically manage potential large vessel hemorrhage or pneumothorax in selected patients. Video-assisted thoracoscopic surgery or simple thoracoscopy^{29,30} can also be useful for visualizing the proximity of endoscopic instruments to major vessels during critical stent placement. If the obstruction is due to malignancy, an oncologist should be included in consultation to contribute to decision-making regarding brachytherapy, external beam radiotherapy, and chemotherapy.

Each member of the team contributes unique, specific knowledge and skill to the process of stent placement. The otolaryngologist provides rigid bronchos-

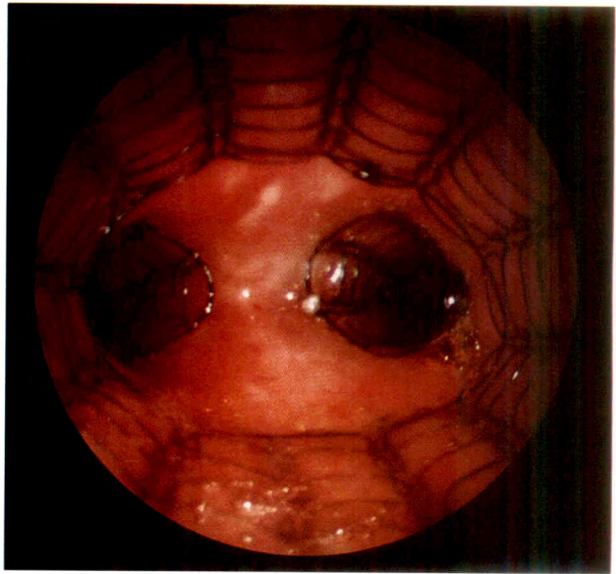


Fig 7. Three Ultraflex stents used to successfully treat severe tracheobronchomalacia without positive pressure ventilation or tracheotomy.

copy through a proximally positioned laryngotracheoscope, use of Nd:YAG and KTP lasers, and use of optical forceps for mechanical debulking. The pulmonologist provides flexible bronchoscopy through the rigid airway to visualize, sample, and treat more distal lesions and is able to perform follow-up examinations to ensure stent patency. Small-diameter flexible bronchoscopy is especially useful in the event that there is a more distal lesion that cannot be seen on initial examination because of the proximal obstruction. The interventional radiologist provides intraoperative fluoroscopic guidance, knowledge of various deployable metal stents and their character-

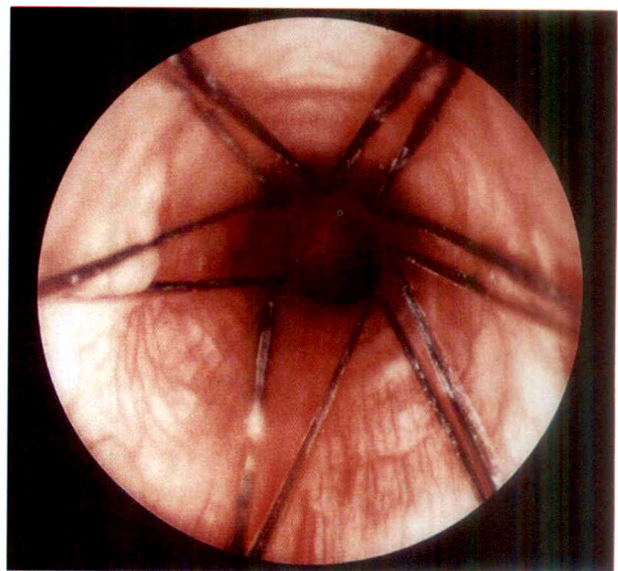


Fig 8. Gianturco stent opens significantly malacic trachea, but leads to undue risk secondary to excessive granulation and migratory tendencies.

COMPARISON OF SEVERAL COMMON AIRWAY STENTS USED IN OUR PRACTICE

Type of Stent	Description	Insertion	Migration Resistance	Granulation Induction	Ease of Removal	MRI-Compatible	Cost
Dumon	Studded silicone tube; fixed diameter	Special rigid bronchoscope	+	++	++++	Yes	\$
Dynamic	Y-shaped silicone with metal struts; fixed diameter	Rigid bronchoscopic placement with special forceps and fluoroscopy	++++	++	++++	No	\$\$\$\$
Wallstent	Self-expanding super alloy wire mesh; fixed diameter	Fluoroscopy with bronchoscopic guidance	++	++	++	No	\$\$\$
Ultraflex	Self-expanding nitinol alloy wire loop mesh; fixed diameter	Fluoroscopy with bronchoscopic guidance	+++	+	++	Yes	\$\$\$
Palmaz	Balloon-expandable stainless steel; expandable diameter	Fluoroscopy with bronchoscopic guidance	+++	+++	++	No	\$\$
Gianturco	Stainless steel wire in radial Z shape; expandable diameter	Fluoroscopy with bronchoscopic guidance	+	++++	+	No	\$

Relative comparisons range from least (+, \$) to greatest (++++, \$\$\$\$).

MRI — magnetic resonance imaging.

istics, and catheter-based techniques for dilation and distal lesion treatment. The multidisciplinary team allows all lesions present to be treated with the most appropriate method of stent delivery.

Although many stents are currently available for use in airway obstruction, no stent is optimal for all types of obstruction. Desirable characteristics of stents include ease of insertion, resistance to migration, a high lumen-to-wall ratio so that the largest possible airway lumen is preserved, a low incidence of granulation tissue formation, and ease of removal. In treating a benign obstruction, a stent that becomes epithelialized and thus facilitates mucociliary clearance may be advantageous if the stent is to be permanent. In benign obstructions in which the stent is to be temporary, a removable stent is obviously advisable. In addition, if the stent is to be used for obstruction due to malacia, it is best to use a flexible stent that is able to contract and expand to withstand the high degree of dynamic stress present in the malacic airway.³¹ For malignant obstructions, in which intraluminal extension of tumor is present or likely, a stent with solid walls or coating is advantageous for preventing tumor ingrowth through the stent. If tumor ingrowth or growth beyond the ends of the stent occurs, it is important to have a stent that is removable or that is not flammable so that a laser can be used to reestablish patency of the airway.

The stents currently available are composed of metal, plastic, or some combination of the two (Fig 1). In general, the plastic stents are older designs limited by a tendency toward migration and secretion retention, while the self-expanding metallic stents are newer designs that to some degree overcome these

limitations.

The most common metal stents include the Palmaz stent, the Wallstent, the Ultraflex stent, and the Gianturco stent (Cook, Bloomington, Ind). The Palmaz stent is a balloon-expandable stainless steel stent, while the other three are self-expanding. The Palmaz stent is helpful in pediatric patients, as it can be progressively dilated as the child's airway grows. However, granulation formation may pose a problem. The Wallstent is a superalloy monofilament wire woven in a mesh and is available with a thin Permalume polymer¹² covering designed to prevent tumor ingrowth. The Wallstent is technically more difficult to place, but incites less inflammatory reaction than the Palmaz stent. The Ultraflex stent is a single nitinol alloy wire woven in a loop shape designed to provide more flexibility with less granulation reaction. It is available with a thin covering designed to prevent tumor ingrowth, exhibits minimal foreshortening on deployment, and incites the least amount of granulation tissue of all the stents. The Ultraflex stent is the only stent with a distal or proximal release mechanism for aid in difficult placements (Fig 7). The Gianturco stent is a stainless steel wire bent in a Z-shape and then formed into a cylinder. Reports of stent fracture, increased granulation, and increased migration coupled with the availability of effective alternatives have made use of the Gianturco stent less common^{32,33} (Fig 8).

The most common plastic stent is the Dumon stent. Other silicone stents include the Dynamic stent. The Dumon stent (modified as the Hood stent in the United States) is a thick-walled silicone tube with externally placed studs that help prevent migration

while allowing the stent to be removed if necessary. A disadvantage of the Dumon stent is its thick walls, which reduce the residual lumen after stenting. This stent is most effectively placed with a specialized rigid bronchoscope delivery system (Dumon Harrel Universal Bronchoscope, Bryan Corporation, Woburn, Mass). The Dumon stent is especially helpful after repair of short-segment tracheal stenoses and as a temporary stent after lung transplantation or homograft tracheal transplant. The Dynamic stent is Y-shaped, with a long tracheal component made up of silicone, with horseshoe-shaped metal struts supporting the anterior portion and a malleable posterior portion that is placed adjacent to the membranous part of the trachea. A specifically designed forceps manufactured by Rusch facilitates Dynamic stent placement. We find the Dynamic stent quite effective for palliative treatment of advanced carcinomas diffusely involving the major airways and carina. The resultant airway is nicely patent, but the rather stiff stent may be uncomfortable to the patient, and mucociliary function is lost over the stented area.

Randomized prospective trials comparing the usefulness of various stents for different clinical applications have not been performed. Therefore, the team

members should choose the optimal stent on an individualized basis depending upon the location and type of the lesion (see Table).

CONCLUSION

Major airway obstruction may be an acutely life-threatening condition. Causes range from congenital anomalies to terminal malignancies, and in many patients, relief of airway obstruction provides a meaningful addition to life expectancy and quality of life, regardless of the underlying cause. The effectiveness of airway stents and other endobronchial methods for the management of airway obstruction has resulted in their broadening use. Much remains to be learned in the expanding field of endobronchial management of airway obstruction, and as knowledge increases, the number of patients who benefit from airway stents is likely to increase. In our experience, the MAST protocol provides a framework for the implementation of the expanding spectrum of endobronchial methods for management of airway obstruction. Otolaryngologists are uniquely qualified to lead MASTs, because of their knowledge of airway management and operative skill, and are encouraged to initiate and organize MASTs at their institutions.

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PEDIATRIC LARYNGOPHARYNGEAL SENSORY TESTING DURING FLEXIBLE ENDOSCOPIC EVALUATION OF SWALLOWING: FEASIBLE AND CORRELATIVE

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Laryngopharyngeal sensory testing can predict aspiration risk in adult patients. Its feasibility and potential role in the evaluation of pediatric swallowing is undetermined. The goals of this study were to determine the feasibility of performing laryngopharyngeal sensory testing in awake pediatric patients and to assess whether the sensory testing results correlated with aspiration during a feeding assessment or correlated with a history of pneumonia. Fiberoptic endoscopic evaluation of swallowing with sensory testing was performed in 100 pediatric patients who were evaluated for feeding and swallowing disorders. The swallowing function parameters evaluated were pooled secretions, laryngeal penetration, and aspiration. The laryngopharyngeal sensory tests were performed by delivering a pressure-controlled and duration-controlled air pulse to the aryepiglottic fold through a flexible laryngoscope to induce the laryngeal adductor response (LAR). The air pulse stimulus ranged in intensity from 3 to 10 mm Hg. The patients tested ranged from 1 month to 24 years of age, with a median age of 2.7 years. Sensory testing was completed in 92% of patients. Patients who had an LAR at less than 4 mm Hg rarely if ever had episodes of laryngeal penetration or aspiration. Those with an LAR at 4 to 10 mm Hg had variable amounts of aspiration and laryngeal penetration. The LAR could not be elicited at the maximum level of intensity (10 mm Hg) in 22 patients, who demonstrated severe laryngeal penetration and/or aspiration. Elevated laryngopharyngeal sensory thresholds correlated positively with previous clinical diagnoses of recurrent pneumonia, neurologic disorders, and gastroesophageal reflux, and correlated positively with findings of pooled secretions, laryngeal penetration, and aspiration. Laryngopharyngeal sensory testing in children is feasible and correlative.

KEY WORDS — aspiration, dysphagia, laryngeal adductor reflex, laryngeal penetration, laryngopharyngeal sensory testing.

INTRODUCTION

Endoscopic evaluation of swallowing was developed as an adjunct to swallowing evaluation in adult patients with dysphagia.^{1,2} This evaluation, commonly known as the flexible endoscopic evaluation of swallowing (FEES), allows for direct visualization of the hypopharynx and larynx during swallowing assessment. Aviv et al^{3,4} developed laryngopharyngeal sensory discrimination testing as an adjunct to the FEES examination for quantifiable determination of the sensory capacity of the laryngopharynx. The swallowing evaluation with sensory testing is known as FEES with sensory testing (FEESST).^{3,4} The initial application of laryngopharyngeal sensory discrimination testing was as a psychophysical test of sensory capacity of the laryngopharynx. As a psychophysical test, the sensation of the laryngopharynx is determined by endoscopically administering

a pressure-controlled (2 to 10 mm Hg) and duration-controlled (50 ms) air pulse stimulus to the mucosa innervated by the superior laryngeal nerve and asking the patient whether he or she feels the stimulus.^{5,6} This test is useful in determining laryngopharyngeal sensory deficits that correlate with aspiration in the adult population^{7,8} after stroke. Laryngopharyngeal sensory discrimination testing is not possible in patients who lack the cognitive skills or the ability to either cooperate with the study or to communicate that they sensed the stimulus, as in adults with neurologic impairments or in infants and young children. To add a more objective dimension to laryngopharyngeal sensory discrimination testing, Aviv et al⁹ tested the laryngeal adductor reflex (LAR), thereby eliminating the need for a conscious and informed response by the patient. The same calibrated puff of air is delivered to the aryepiglottic fold region of the larynx.

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Stimulation to this region induces the involuntary LAR. The resulting response is a brief closure of the vocal cords with or without a swallow. Adult thresholds and ranges in stimulus intensity are established and correlate with aspiration risk. A patient is considered to have a normal result if the LAR can be elicited at less than 4 mm Hg of air pulse pressure. A patient is considered to have a moderate laryngopharyngeal sensory deficit if the LAR is elicited between 4.0 and 6.0 mm Hg. The patient is considered to have a severe sensory deficit if the LAR is elicited at greater than 6.0 mm Hg.⁹ The advantage of this test is that it can be performed in patients who cannot provide a subjective response or who lack the cognitive functional ability to cooperate.

The FEES technique has been used in pediatric patients for evaluation of swallowing and feeding disorders.¹⁰ The role and feasibility of laryngopharyngeal sensory testing as an adjunct to the pediatric FEES evaluation has not been determined. The goal of this study was twofold: to determine whether laryngopharyngeal sensory stimulation testing could be performed in awake pediatric patients, and to determine whether the sensory information obtained correlates with the observation of laryngeal penetration and/or aspiration seen during a feeding assessment, or with a history of medical diagnosis of pneumonia, neurologic disorder, or gastroesophageal reflux.

PATIENTS AND METHODS

Evaluation Protocol. The FEES examination was performed in infants and children evaluated for feeding disorders, dysphagia, or anatomic upper airway abnormalities, or as part of the routine evaluation before airway reconstructive surgery. Sensory testing was performed after the FEES examination. A pediatric otolaryngologist and a speech and language pathologist (SLP) with expertise in pediatric dysphagia performed the examination. The SLP determined the consistencies for the feeding evaluation and either fed the patient or interacted with the caretaker during the endoscopic feeding assessment. The otolaryngologist performed the endoscopic portion of the procedure. The swallowing assessment and determination of feeding parameters were performed jointly by the SLP and otolaryngologist. The procedure was performed with the patient awake and in an upright position. This usually required gentle restraint of the infant or child by having the child sit in the lap of a caregiver or assistant who placed his or her arms around the child. Occasionally, another assistant was needed to hold the patient's head. A topical nasal anesthetic was applied. A flexible laryngoscope (3.2-mm diameter) with a separate internal port for air pulse delivery (FNL 10 AP Laryngoscope, Pentax Precision Instru-

ments Corp, Orangeburg, NY) was introduced into the nose and advanced until the laryngopharyngeal structures were visualized. The degree of pooling of hypopharyngeal secretions was evaluated and recorded as none, minimum, moderate, or severe. A swallowing assessment was performed with liquids and with a variety of textures, if developmentally appropriate. Formula, liquids, or foods similar to the patient's current diet were dyed with green food coloring to aid in visualization. The feeding parameters evaluated in this study were laryngeal penetration and aspiration and were documented as either present or absent. If the child had severely limited oral or motor skills and/or significant oral aversion, green food coloring was introduced into the mouth to stain the secretions to observe the path of the patient's own secretions in the hypopharynx during respiration and voluntary or induced swallow. Laryngeal penetration or aspiration of secretions could be observed in these patients, but because there was no actual feeding and swallowing evaluation, these patients were not included in statistical evaluations of swallowing parameters. These patients were categorized as "could not test." During the swallowing function assessment, if significant laryngeal penetration occurred, the feeding assessment was stopped to prevent further aspiration events. After the feeding assessment, the SLP recorded the amount of pooled secretions, as well as the presence or absence of aspiration as determined by both the otolaryngologist and the SLP.

After completion of the feeding evaluation, laryngopharyngeal sensory stimulation testing was performed. The distal tip of the laryngoscope was positioned so that it was approximately 2 to 4 mm from the test site. The air pulse was delivered to the aryepiglottic fold region of each side of the laryngopharyngeal complex (right and left) separately, via the internal air channel, with the air pulse being generated by an air pulse sensory stimulator device developed for this purpose (AP-4000 Air Pulse Sensory Stimulator, Pentax). The air pulse was 50 ms in duration and varied in intensity from 3 to 10 mm Hg, starting from 3.0 mm Hg and sequentially increased in increments of 0.5 mm Hg until the LAR was induced. A brief, nonrhythmic break in respiration or a cough response with or without a swallow response was considered a positive response to stimulation. The level of intensity required to induce the response was recorded for each side in all patients. Notation was made of any patient in whom the LAR could not be induced at the maximum output of the stimulation device (10 mm Hg). For statistical purposes, patients in this group were assigned an LAR air pulse threshold of 10 mm Hg.

The history and medical records of all patients

TABLE 1. DEMOGRAPHICS OF PATIENTS WHO UNDERWENT LPST TESTING

	<i>Patients (n = 100)</i>
Male	70
Female	30
Mean age (y)	5
Median age (y)	2.7
FEESST parameters	
Hypopharyngeal secretions	
None	48
Minimal	21
Moderate	9
Severe	22
Laryngeal penetration	
No	50
Yes	46
Could not test	4
Aspiration	
No	65
Yes	31
Could not test	4
LAR	
Present	78
Absent	22
Medical diagnoses	
Recurrent pneumonia	
No	74
Yes	26
Neurologic diagnosis	
No	67
Yes	33
Gastroesophageal reflux	
No	75
Yes	25

LPST — laryngopharyngeal sensory threshold, FEESST — fiberoptic endoscopic evaluation of swallowing with sensory testing, LAR — laryngeal adductor response.

were reviewed to determine whether there was a history of recurrent pneumonia, an underlying neurologic disorder, or a history of gastroesophageal reflux disease. Neurologic diagnoses included hypotonia, cerebral palsy, mental retardation, central hypoventilation syndrome, seizure disorder, Chiari malformation, stroke, cranial neuropathy, and birth asphyxia. A diagnosis of gastroesophageal reflux was considered positive if documented either by a pH probe or on a barium swallow study.

Statistical Analysis. Patient demographics were evaluated by determining the mean age and standard deviation and the median age of patients who underwent sensory testing.

The mean air pulse threshold required to induce the LAR was determined for the right and left sides

separately. A paired *t*-test was used to determine whether there was a statistical difference between the right and left sides. The air pulse stimulus required to induce the LAR on the right and left sides was determined for each patient. The individual patient values from the right and left sides were averaged, and this number was used for the remainder of the statistical analysis.

The Mann-Whitney U test was used to determine whether there was a difference in the air pulse intensity required to induce the LAR in patients with a clinical diagnosis of recurrent pneumonia, neurologic disorder, or gastroesophageal reflux. An analysis of variance was used to determine whether there was a difference between the degree of hypopharyngeal secretion pooling and the air pulse intensity required to induce the LAR. An analysis of variance was also used to determine whether there was a difference between the presence or absence of laryngeal penetration or aspiration and the air pulse intensity required to induce the LAR. A Bonferroni-Dunn correction was used to analyze between-group differences if the results of the analysis of variance were significant.

Contingency tables using a χ^2 analysis were used to determine whether the absence of the LAR correlated with a finding of laryngeal penetration and aspiration or a medical diagnosis of pneumonia, neurologic disorder, or gastroesophageal reflux. Contingency tables with a χ^2 analysis were also used to determine whether there was a correlation between pooled hypopharyngeal secretions and the same findings. All statistical analyses were performed with the StatView statistical software package (SAS Institute, Cary, NC).

RESULTS

Between November 1997 and January 1999, a total of 108 infants and children underwent FEESST. Sensory testing was performed successfully in 92.5% of the patients. Sensory testing could not be performed in 8 of the 108 patients (7.5%) because of anatomic findings that prevented accurate testing in 2 patients and because of excessive gagging or crying in 6 patients. As shown in Table 1, 100 patients completed sensory testing; 30 were girls and 70 were boys. Their ages ranged from 1 month to 24 years, with a median age of 2.7 years and mean age of 5 years. Of these 100 patients, pooled hypopharyngeal secretions were present in 52 patients and were described as minimal in 21, moderate in 9, and severe in 22. Forty-eight patients had no pooled secretions. Ninety-six patients were able to comply with the swallowing portion of the assessment; 46 patients demonstrated laryngeal penetration, and 31 demonstrated aspiration. These parameters were not assessed in 4 pa-

TABLE 2. MEAN LPST REQUIRED TO INDUCE LAR IN PATIENTS WITH AND WITHOUT UNDERLYING DIAGNOSES

	<i>Pneumonia</i>		<i>Neurologic Disorder</i>		<i>Gastroesophageal Reflux</i>	
	<i>Yes</i> (<i>n</i> = 26)	<i>No</i> (<i>n</i> = 74)	<i>Yes</i> (<i>n</i> = 33)	<i>No</i> (<i>n</i> = 67)	<i>Yes</i> (<i>n</i> = 25)	<i>No</i> (<i>n</i> = 75)
LPST (mm Hg)	7.4 ± 2.8	4.5 ± 2.5	7.4 ± 2.8	4.2 ± 2.3	6.3 ± 2.9	4.9 ± 2.8
<i>p</i>	<.0001		<.0001		.02	

χ^2 for correlation: *p* = .008 for pneumonia and neurologic disorder; *p* = .01 for pneumonia and gastroesophageal reflux; and *p* = .11 for neurologic disorder and gastroesophageal reflux.

tients with severely limited oral motor skills or oral aversion who were uncooperative with the swallowing evaluation. There was a history of recurrent pneumonia in 26 patients, an underlying neurologic disorder in 33 patients, and a history of gastroesophageal reflux in 25 patients.

The LAR could be induced by air pulse stimulation in 78 patients. There was no statistical difference in the laryngopharyngeal sensory threshold (LPST) intensity required to induce the LAR between the right side (5.28 mm Hg) and the left side (5.31 mm Hg). There was a subgroup of 22 patients who had no LAR even with the maximum output of the sensory stimulation device (10 mm Hg). For statistical purposes, these patients were assigned an LPST of 10 mm Hg. The combined laryngopharyngeal air pulse thresholds ranged from 3 to 10 mm Hg, with a mean of 5.3 ± 2.8 mm Hg and a median of 3.5 mm Hg.

Underlying clinical diagnoses were associated with an increase in LPST, as shown in Table 2 and Fig 1. Patients with a history of recurrent pneumonia had a higher LPST, 7.4 ± 2.8 mm Hg, compared with an LPST of 4.5 ± 2.5 mm Hg in patients with no history of pneumonia (*p* < .0001). Those with an underlying neurologic diagnosis had a higher LPST, 7.4 ± 2.8 mm Hg, compared with an LPST of 4.2 ± 2.3 mm Hg in patients with no neurologic disorder (*p* < .0001). Patients with a diagnosis of gastroesophageal reflux also had a higher LPST, 6.3 ± 2.9 mm Hg, compared

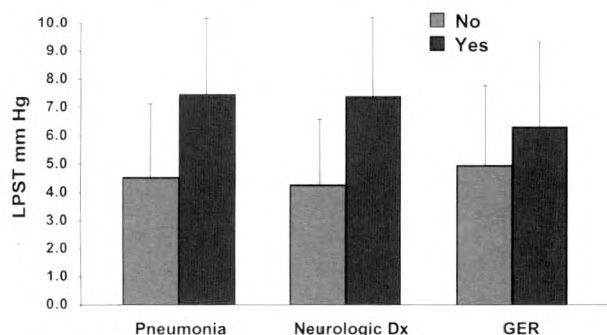


Fig 1. Bar graph displays mean laryngopharyngeal sensory threshold (LPST) air pulse intensity required to induce laryngeal adductor reflex (LAR) in patients with (yes group) and without (no group) history of recurrent pneumonia, underlying neurologic diagnosis (Dx), or gastroesophageal reflux (GER).

with an LPST of 4.9 ± 2.8 mm Hg in patients with no known diagnosis of gastroesophageal reflux (*p* = .02). In addition, there was a positive correlation between a history of recurrent pneumonia and the presence of an underlying neurologic disorder (*p* = .008), and between recurrent pneumonia and gastroesophageal reflux (*p* = .01).

The findings of pooled secretions, laryngeal penetration, and aspiration correlated with increased LPST. As shown in Fig 2, increasing amounts of pooled hypopharyngeal secretions paralleled an incremental increase in the LPST. There was no statistical difference between the LPST of 3.5 ± 1.5 mm Hg found in patients who had no secretions and the LPST of 3.8 ± 1.1 mm Hg found in patients who had minimal amounts of pooled secretions. There was, however, a difference in the LPST in patients with no secretions or minimal secretions and the LPST of 7.5 ± 2.3 mm Hg found in patients with moderate pooling of secretions (*p* < .0001) and the LPST of 9.5 ± 0.9 mm Hg found in patients with severe pooling of secretions (*p* < .0001). There was also a difference in the LPST in patients with moderate pooling of secretions as compared with those with severe pooling of secretions (*p* < .0001). As shown in Table 3 and Fig 3, there was a difference between the LPST of 7.3 ± 2.8 mm Hg found in patients with laryngeal penetration and the LPST of 3.4 ± 1.1 mm Hg found in patients without laryngeal penetration seen during the feeding assessment (*p* < .0001). Patients who demonstrated aspiration during the feeding assessment likewise had a higher LPST, 8.5 ± 2.2 mm Hg, compared with an LPST of 3.8 ± 1.6 mm Hg in patients who did not have aspiration (*p* < .0001).

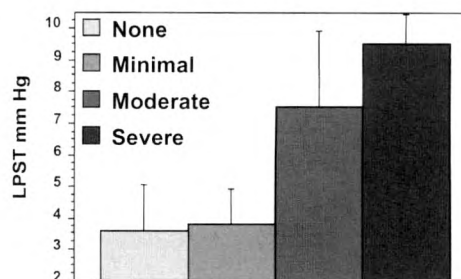


Fig 2. Bar graph displays mean LPST air pulse intensity required to induce LAR in relation to amount of pooled hypopharyngeal secretions.

TABLE 3. MEAN LPST IN PATIENTS WITH AND WITHOUT FINDINGS OF LARYNGEAL PENETRATION AND ASPIRATION ON FEES

	Laryngeal Penetration		Aspiration	
	Yes (n = 46)	No (n = 50)	Yes (n = 31)	No (n = 65)
LPST (mm Hg)	7.3 ± 2.8	3.4 ± 1.1	8.5 ± 2.2	3.8 ± 1.6
p	<.0001		<.0001	

FEES — fiberoptic endoscopic evaluation of swallowing.

As shown in Table 4, there was a correlation between the finding of pooled hypopharyngeal secretions and laryngeal penetration ($p < .0001$), aspiration ($p < .0001$), recurrent pneumonia ($p < .0001$), and neurologic disorders ($p = .002$).

Also shown in Table 4, the LAR was absent and could not be elicited at the maximum intensity of the stimulus delivery device in 22 patients. The absence of an LAR correlated strongly with the feeding parameter findings of laryngeal penetration ($p < .0001$) and aspiration ($p < .0001$) and correlated with the diagnosis of a neurologic disorder ($p < .0001$) and a history of recurrent pneumonia ($p = .004$).

DISCUSSION

Infant and pediatric feeding and swallowing disorders result from a different spectrum of disease processes than do adult disorders; however, intact airway protection is essential to prevent aspiration in both patient groups. Laryngopharyngeal sensory testing has proven to be a useful adjunct for evaluation of airway protective mechanisms in adult patients. Laryngopharyngeal sensory testing evaluates the integrity of the airway protective reflex mechanisms. The LAR is activated by mechanical or chemical stimulation of the supraglottic mucosa in the region of the aryepiglottic fold.¹¹⁻¹⁴ Sensory information is

TABLE 4. STATISTICAL CORRELATIONS

	Pooled Secretions (n = 52; χ^2 p value)	Absent LAR (n = 22; χ^2 p value)
Laryngeal penetration (n = 46)	<.0001	<.0001
Aspiration (n = 31)	<.0001	<.0001
Pneumonia (n = 26)	<.0001	.004
Neurologic disorder (n = 33)	.002	<.0001
Gastroesophageal reflux (n = 25)	.07	.16

transmitted through the superior laryngeal nerve via the special visceral afferent fibers of the vagus nerve to the inferior (nodose) ganglion. From there, information is sent to the nucleus solitarius, the brain stem nucleus responsible for regulation of swallowing and respiration. The efferent response initiated at the nucleus ambiguus results in glottic closure and inhibition of respiration with or without a swallow. An intact LAR indicates that the reflex arc is intact, whereas a depressed or absent LAR may indicate an inability to sense or recognize secretions and food in the laryngopharynx, which can lead to poor initiation of the laryngeal protective reflex.^{15,16} Thus, an unrecognized sensory deficit would be expected to lead to an increased likelihood of laryngeal penetration, aspiration, and subsequent development of pneumonia.

The FEES technique has been successfully used for evaluation of pediatric swallowing disorders.¹⁰ We have now demonstrated that sensory testing can be relatively safely added to the pediatric evaluation. In the evaluation of swallowing disorders, LPST testing offers an advantage over a modified barium swallow study by providing a measure of the sensory capacity of the larynx and also provides an assessment of the ability to protect the airway through the generation of the glottic closure response.

As seen in adults, pediatric patients with an increased LPST have a significantly higher likelihood of having laryngeal penetration and aspiration during a feeding assessment.⁸ Prospective assessments of sensory testing in pediatric patients will be required to determine whether an increased LPST is predictive of aspiration risk and its complications. Comparable to the previously studied adult population, there is a correlation between a history of an underlying neurologic disorder and an increased LPST.⁷⁻⁹ Our study population differs from the adult series in that there were various underlying neurologic diagnoses other than stroke. Although retrospectively documented, pediatric patients with an increased LPST had a significantly increased likelihood of having a history of recurrent pneumonia. We also found a positive correlation between a history of gastroesophageal reflux disease and an increased LPST. It is plausible

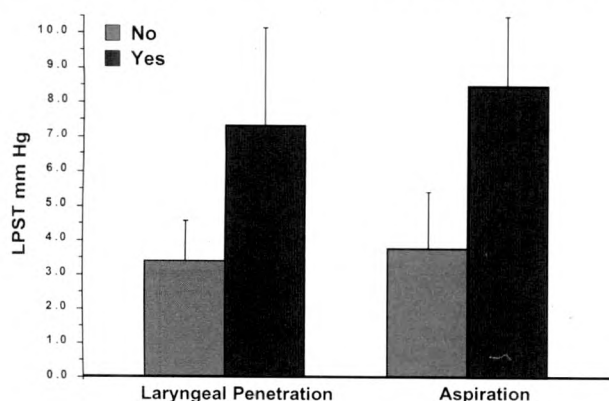


Fig 3. Bar graph displays mean LPST air pulse intensity required to induce LAR in patients with (yes group) and without (no group) laryngeal penetration and aspiration as determined by feeding evaluation.

that chronic laryngeal reflux injury alters the sensory capacity and the resultant glottic closure response of the larynx, analogous to the alteration of the pharyngo–upper esophageal sphincter contractile reflex seen in adult patients with posterior laryngitis from gastroesophageal reflux.¹⁷

The assessment of pooled secretions in the hypopharynx is part of the routine FEES examination. Inability to control the secretions and clear the hypopharynx is known to increase the likelihood of aspirating food or liquids.¹⁸ We found that the presence of pooled secretions in children with a feeding or swallowing disorder predisposes them to having laryngeal penetration and aspiration during feeding. We likewise found that pooled secretions correlated with a history of pneumonia — this has not been statistically substantiated in adults or children until now. The findings of our present study show a significant difference in the amount of pooled secretions that corresponds to an incremental increase in the LPST, implying that altered laryngopharyngeal sensation results in inability to clear secretions. Our findings of decreased sensation and pooled secretions are in concordance with those of other studies that show that patients who accumulate secretions in the hypopharynx have dampened laryngopharyngeal protective reflexes.¹⁶ We also found a strong correlation between neurologic disorders and increased pooling of secretions. This finding may not only be the result of a sensory deficit, but also could result from an inability to clear secretions because of a motor impairment. The finding of pooled secretions in the hypopharynx in children with feeding and swallowing disorders should heighten the suspicion of altered airway protection capability and the likelihood of developing aspiration and pneumonia if the child is unable to clear the secretions with a swallow.

In contrast to previous adult studies, this study separated out a group of 22 patients with swallowing dysfunction in whom an LAR could not be elicited even at maximal stimulation intensity. This inability not only indicates a severe sensory deficit, but also demonstrates altered ability to close the glottis and protect the airway in response to a stimulus. We found that children in whom the LAR was absent even under maximal stimulation had laryngeal penetration and aspiration during feeding and had a strong correlative history of recurrent pneumonia and an underlying neurologic disorder. Any patient in whom the LAR cannot be elicited should be considered to have poor airway protective capability, and a neurologic disorder should be considered if not previously diagnosed. It is conceivable that LPST testing is not only a valid assessment of the neurosensory capacity of

the larynx, but also a means of assessing the airway protective capacity of the larynx. It is difficult to precisely determine whether the absence of LAR seen in these children is primarily a sensory afferent response failure, an efferent motor failure, or a combination of both. Because most of these children have vocal cord movement with phonation or crying, it would seem that an absent LAR is a sensory failure. The sensory component is difficult to evaluate in children, because some are not capable of participating in a subjective response. Simultaneous LPST testing with studies of central responses in children will be required to answer this question.

This study evaluated parameters of our clinical practice of FEES with the addition of sensory testing. Since 1993, more than 600 FEES examinations have been performed at our institution, where our practice standard is for the SLP and otolaryngologist to rate and discuss the evaluative parameters of pooled secretions, laryngeal penetration, and aspiration jointly. Future studies that evaluate the utility of this technique in children should address any potential interobserver variability in rating these parameters. Even though more than 300 sensory evaluations of the larynx in children have been performed at our institution by 2 otolaryngologists, the authors recognize that there may be variability in the test when performed at different times or by different examiners based on the experience of the endoscopist with sensory testing and on patient factors. Some bias may also have been introduced to the study interpretation because the feeding observation was performed before the sensory testing, but the consistency of right-side versus left-side sensory testing seen in this study suggests that the observed response is rather objective. Future studies will need to address the potential examiner variability of pediatric sensory testing. This cross-sectional evaluation of our clinical practice does not allow for critical assessment of a potential intraobserver bias, which should be a goal for future studies that evaluate applications of FEES and sensory testing in the pediatric population.

CONCLUSION

We have demonstrated that FEESST can be relatively safely performed in the infant and pediatric population. As in adults, a reduced laryngopharyngeal sensory capacity correlated with laryngeal penetration and aspiration during a feeding evaluation in children. Reduced laryngopharyngeal sensory capacity likewise correlated with a history of pneumonia, neurologic disease, and gastroesophageal reflux. The finding of pooled secretions in the hypopharynx on flexible endoscopy in children with underlying feeding and swallowing disorders should heighten clinical

cian awareness of the potential for laryngeal penetration and/or aspiration and alteration of airway protection, and should prompt further investigation to determine the clinical significance. An absent LAR in response to stimulation signifies severe alteration in the sensory capacity of the larynx and altered airway protection ability.

Children with dysphagia and feeding disorders typically require multiple evaluations to determine dietary and behavioral management. This testing method has the potential ability to follow the progression or regression of feeding and swallowing function and

airway protective capability without repeated exposure to radiation. Studies are currently under way to compare this technique with videofluoroscopic swallowing evaluation. These studies, along with disease outcome evaluations, will be necessary for determining where FEESST truly belongs in the armamentarium of evaluating feeding and swallowing disorders in children. As the application of sensory testing extends to include medically diverse populations of patients, we will find broader applications of the technique and further our understanding of airway protection as it relates to deglutition, neurologic disease, gastroesophageal reflux, and pneumonia.

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EVALUATING LARYNGOTRACHEAL STENOSIS IN A CANINE MODEL WITH VIRTUAL BRONCHOSCOPY

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We performed a prospective masked animal study to determine whether virtual bronchoscopy, a noninvasive computed tomography technique, can accurately measure upper airway stenosis. Virtual bronchoscopy creates a 3-dimensional endoscopic image from spiral computed tomography data. Laryngotracheal stenosis was endoscopically induced in 18 dogs. The excised larynges were examined by endoscopy, virtual bronchoscopy, and macrodissection. Measurements were made of the anteroposterior (A-P) diameter, the left-right (L-R) diameter, the full length of stenosis in the sagittal plane, and the length of the tightest stenotic segment. Each measurement method was performed independently. All investigators were unaware of measurements made by others. The measurements obtained through virtual bronchoscopy and actual endoscopy were compared to those made at dissection by interclass correlation coefficients (ICCs). Endoscopy was better than virtual bronchoscopy in measuring the A-P diameter ($ICC = .79, p < .0001$; $ICC = .42, p = .01$). Both were equally effective in measuring the L-R diameter ($ICC = .53, p = .0062$; $ICC = .52, p = .0064$). The endoscopes could not assess the full length of the stenosis, whereas virtual bronchoscopy measured it fairly accurately ($ICC = .72, p = .0001$). Virtual bronchoscopy relatively accurately measured the length of the tightest stenotic segment ($ICC = .68, p = .0002$), whereas endoscopy produced measurements in only 11 of 18 larynges, and the measurements were less accurate ($ICC = .45, p = .0068$). Virtual bronchoscopy can provide good measurements of stenotic lesions in the airway. It is more accurate than actual endoscopy in determining the length of stenosis. It may therefore be useful as an adjunct imaging method in preoperative planning for reconstructive surgery.

KEY WORDS — laryngotracheal reconstruction, laryngotracheal stenosis, spiral computed tomography, subglottic stenosis, virtual bronchoscopy.

INTRODUCTION

Three-dimensional (3-D) "virtual bronchoscopy" (VB) is a new, noninvasive technique for performing a simulated endoscopy that produces images of endoluminal structures similar to the images seen in actual endoscopic examinations. Thin-section computed tomography (CT) helical data are reformulated to present a realistic surface rendering of the inner walls of the airway or of other hollow structures.¹⁻²¹

Although this technique has excited interest, the role of 3-D VB in patients with pathological lesions of the upper airway has not yet been defined.

Three-dimensional VB is now performed routinely at the Cleveland Clinic Foundation to evaluate patients with complicated upper airway disorders, especially those suffering from laryngotracheal stenosis (LTS) who plan to undergo laryngotracheal reconstruction (LTR). Our clinical experience suggested that preoperative VB made accurate measurements

of the severity and the length of the LTS, thereby enabling better planning of the LTR. This hypothesis was studied in a canine model.

MATERIALS AND METHODS

The study was approved by the Animal Research Committee of the Cleveland Clinic Foundation, and the animals received humane care in compliance with *The Principles of Laboratory Animal Care*, formulated by the National Society for Medical Research, and the *Guide for the Care and Use of Laboratory Animals*, prepared by the National Academy of Sciences.

INDUCTION OF LARYNGOTRACHEAL STENOSIS

Laryngotracheal stenosis was induced by a previously proven technique²² in 18 mongrel dogs (*Canis familiaris*), each weighing between 7 and 10 kg. Each dog was anesthetized with intramuscular ketamine hydrochloride (20 mg/kg) and intramuscular xylazine

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Fig 1. Endoscopic view of stenosed larynx. Tip of endoscope is placed at level of true vocal cords.

hydrochloride (1.5 mg/kg) and placed in the supine position. Its mouth was kept open with a bite blocker, and the tongue was extended and secured with a strip of gauze tied to the bite blocker. The exposed larynx was sprayed with Cetacaine topical anesthetic spray (Cetylite Industries Inc, Pennsauken, NJ), and the epiglottis was lifted with the tip of a 3.5-mm 30° Hopkins telescope (Karl Storz Endoscopy, Culver City, Calif) connected through a video camera to a monitor. The junction between the lower part of the cricoid cartilage and the upper part of the first tracheal ring was then injured by electrocautery by means of a curved insulated suction-cautery tip connected to a standard Bovie electrosurgical cautery unit and operated at 40 power units. The mucosa and underlying cartilage were injured at 4 equally spaced points by means of 2- to 3-second exposures.

The dogs were then observed for a period of up to 21 days. At any sign of airway obstruction or at day 21, the animals were humanely sacrificed with intravenous pentobarbital sodium (75 mg/kg), and a laryngectomy was performed.

ENDOSCOPIC EXAMINATION AND VIDEO DOCUMENTATION

Four measurements were made in the excised larynges (Fig 1): the anteroposterior (A-P) and left-right (L-R) diameters of the narrowest subglottic lumen, the full length of stenosis (FL) in the sagittal plane (ie, from the most superior border of the lesion to its most inferior border), and the length of the tightest stenosis (TS). To ensure consistency in the A-P and L-R measurements, the tip of the telescope was always positioned at the plane of the free edges of the true vocal cords. If the endoscope could pass through the stenotic segment, the FL and TS were measured against markings on the endoscope.

The videotaped examination was reviewed in a computerized laboratory by means of Adobe Photo-

shop 4.0 and Illustrator 6.0 software (Adobe Systems Inc, San Jose, Calif). The results of the A-P and L-R measurements were divided by a factor of 2.2, which was found to give actual dimensions in prior testing (unpublished observations).

VIRTUAL BRONCHOSCOPY

Cross-sectional Imaging. Cross-sectional imaging (Fig 2) was performed on a Siemens Medical Systems Somatom Plus 4 spiral CT scanner (Erlangen, Germany). Each specimen was placed supine with the long axis of the airway parallel to the long axis of the patient table. This setup permitted axial imaging of the airway. All scans were done at an x-ray tube potential of 120 kilovoltage peak, an x-ray tube current-time product of 292 mA, and a gantry rotation speed of 360°/s. The ray beam collimation was 1 mm, and the table speed was 1 mm/s, yielding a pitch of 1.0. The 1-mm-thick images were contiguous without overlap, because the 3-D software could not deal with fractional slice thickness (ie, 0.5 mm). The images were reconstructed with a 75-mm field of view, with an image-plane reconstruction algorithm AB (adult body) 50 and a 180° linear z-axis interpolation algorithm. The images were transferred electronically to a workstation for postacquisition processing.

Three-dimensional Rendering. The axial images were rendered into 3-D composite images by means of a hardware-software package (3D Virtuoso, Siemens Medical Systems). The package allows the user to select which CT values and Hounsfield units (HU) are included in the image and which are eliminated. For this study, the level was -200 HU, so air appeared as dark gray. The window width was 1,000 HU (-700 HU is black and +300 HU is white). This setting permitted visualization of air, soft tissue, and bone on the same image. The software was then put into a 4-window viewing mode so the airway could be simultaneously viewed as axial, sagittal, and coronal cross sections and as a 3-D VB image. In the VB mode, the airway was seen from the viewpoint of the tip of an endoscope. The viewpoint could be advanced, retracted, translated, and rotated so that any surface could be viewed. The field of view could also be changed. At all times, the location of the viewpoint was displayed on the images of the axial, sagittal, and coronal planes, and the location was updated at a rate of 5 to 8 frames per second.

Measurement Methods. The virtual bronchoscope was advanced through the lumen in the cranial-caudal direction. When the region of maximum stenosis was reached, distance caliper points were inserted into the image by means of the software's distance measurement tool. The two ends of the distance tool

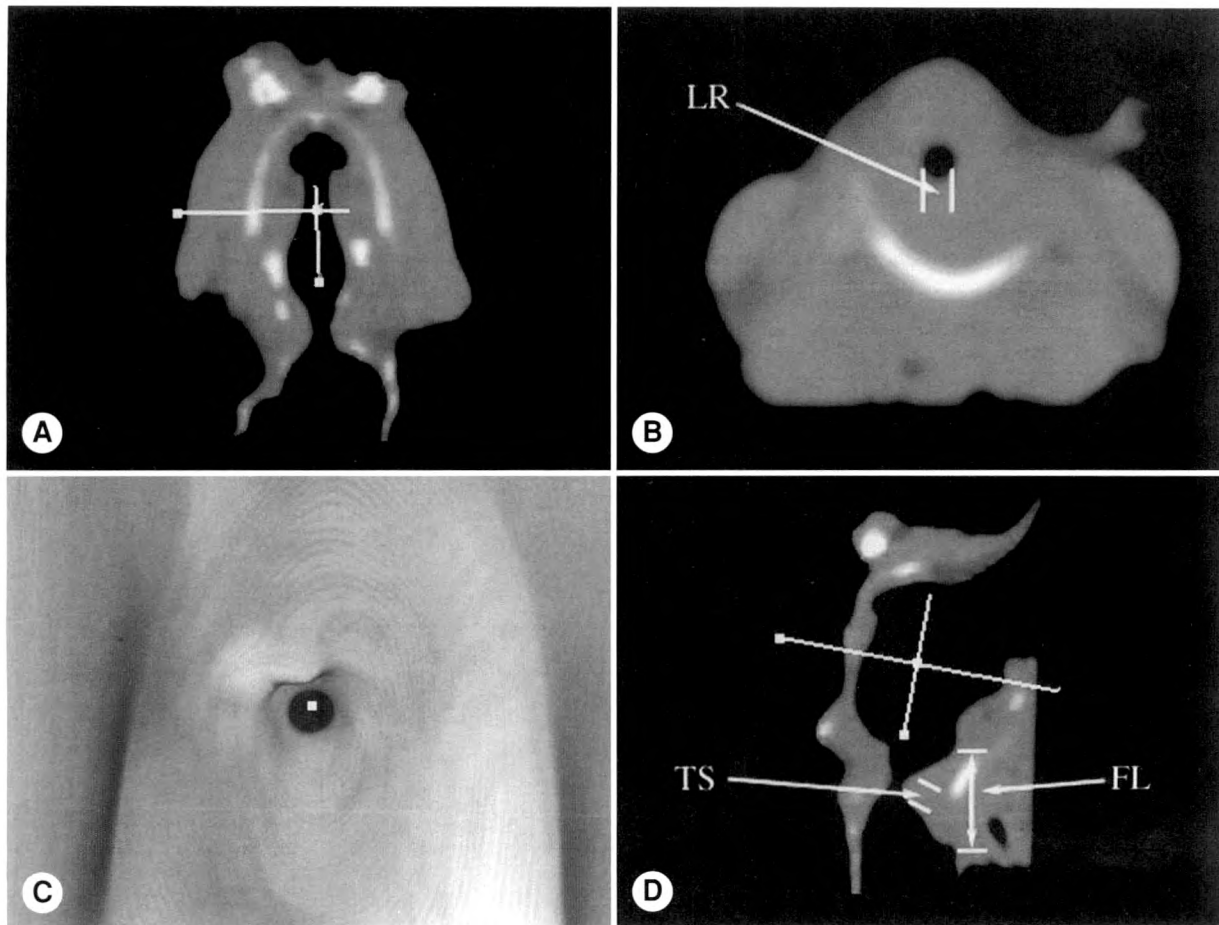


Fig 2. Spiral computed tomography scan of stenosed larynx after laryngectomy. Multiplanar reconstruction mode is used, in which axial, coronal, sagittal, and "fly-through" views are all displayed simultaneously, and pattern and direction of "scope" are shown continuously. A) Coronal view. B) Axial view. LR — left-right. C) Virtual bronchoscopy. D) Sagittal view. TS — length of tightest stenosis, FL — full length of stenosis.

were placed so that they abutted the interior wall of the airway. The placement of the distance tool was then confirmed in the 2-dimensional (2-D) images. The FL was measured by placing the cranial end of the distance tool at the first location in which the caliber of the airway seemed to deviate from normal as judged from the VB view. The caudal end of the distance tool was placed at the location in which the caliber of the airway returned to normal. This tool placement was then confirmed and finely adjusted on the 2-D images. The TS was measured by placing one end of the distance tool at the place in the airway in which the caliber ceased to decrease and either remained constant or increased. The other end of the distance tool was placed at the location in which the narrowest stricture started to expand. Again, the distance measurement tool placement was confirmed and finely adjusted on the 2-D images. Similar methods were used to measure the A-P and L-R diameters.

PATHOLOGICAL EXAMINATION

After all endoscopic and VB measurements were

made, the larynx was sectioned horizontally just below the location in which the narrowest stricture was seen (Fig 3). The A-P and L-R diameters of the narrowest lumen were measured. The larynx was then sectioned longitudinally through the posterior midline aspect. The FL in the sagittal plane, and the TS were measured.

STATISTICAL ANALYSIS

The results obtained by VB and by actual endoscopy were compared to the pathological results, which were considered the "gold standard," with interclass correlation coefficients (ICCs). The ICC measures the level of agreement between different continuous measures of the same observational units. The closer the ICC is to 1, the better the agreement between the two sets of measures. The closer the ICC is to 0, the worse the agreement. The p value represents the probability that no association exists between the sets of measures.²³ A p value of <.05 was considered as significant.

RESULTS

All 18 dogs developed LTS and were included in

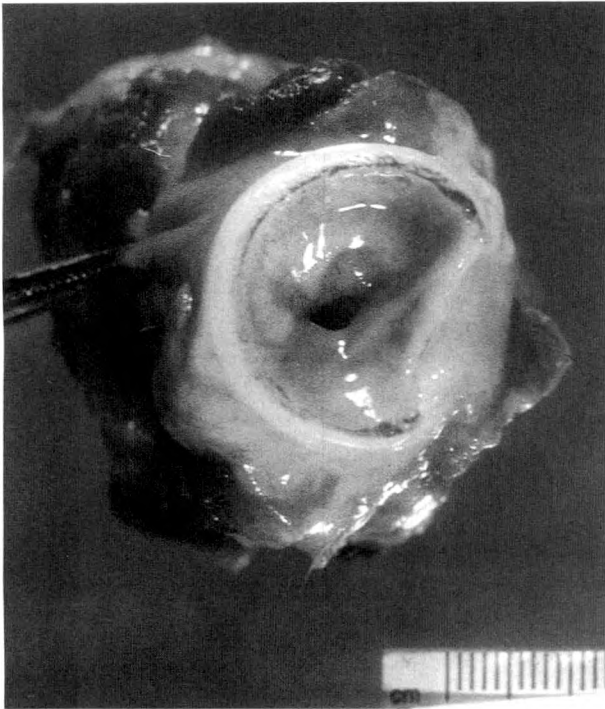


Fig 3. Macroscopic specimen of stenosed larynx, viewed from below.

the study. The results of statistical analysis are shown in the Table, and the mean error from pathological measurements (in millimeters) is shown in Fig 4.

Endoscopy was better than VB at measuring the A-P diameter ($ICC = .79$, $p < .0001$; $ICC = .42$, $p = .01$, respectively). Both were equally accurate in identifying the L-R diameter ($ICC = .53$, $p = .0062$; $ICC = .52$, $p = .0064$). Endoscopy was not able to evaluate the FL, whereas VB measured it fairly accurately ($ICC = .72$, $p = .0001$). Virtual bronchoscopy measured the TS reasonably well ($ICC = .68$, $p = .0002$), whereas endoscopy was able to identify it only in 11 of 18 dogs and with less accuracy ($ICC = .45$, $p = .0068$).

CASE REPORT

After prolonged intubation due to a cerebrovascular accident, a 66-year-old patient developed subglottic and tracheal stenosis. A metallic expandable stent was inserted into the stenotic region in another hospital. Five days before the current imaging study, the patient began to suffer from difficulty in breathing on exertion. The findings on physical examination

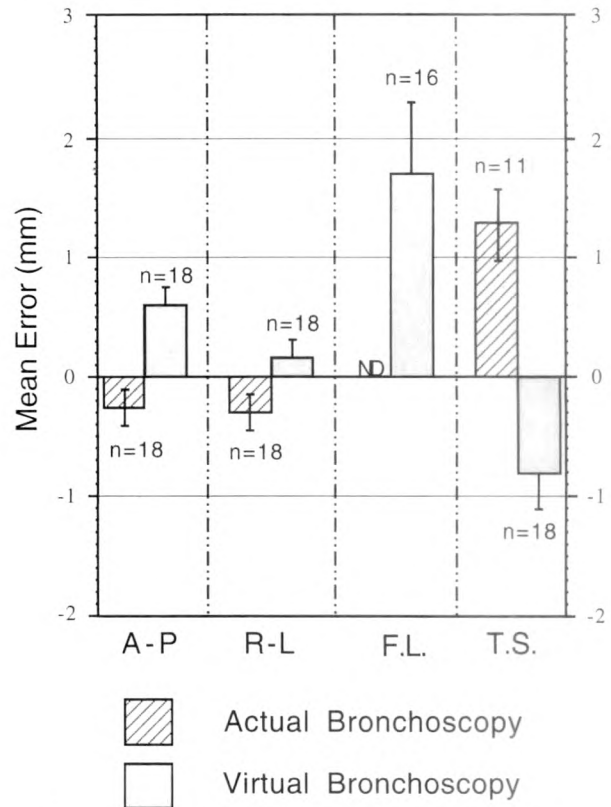


Fig 4. Mean error from pathological measurements (in millimeters). ND — not done, A-P — anteroposterior diameter, R-L — right-left diameter, F.L. — full length of stenosis, T.S. — tightest stenosis.

and fiberoptic laryngoscopy were normal. It was not possible to pass the endoscope through the vocal cords. A 3-D spiral CT scan was then performed. It revealed obstruction of the upper part of the stent by a lesion, which was found later to be granulation tissue (Fig 5). Virtual bronchoscopy clearly demonstrated that the lower part of the stent was without evidence of significant luminal compromise. It also accurately delineated the relationship between the stent and the walls of the airway. The remaining luminal cross-sectional area and the length of the obstructing lesion were readily measured. After this examination, the patient underwent bronchoscopy with neodymium:yttrium-aluminum-garnet laser resection of granulation tissue. All measurements previously obtained were found to be accurate.

DISCUSSION

Virtual bronchoscopy is a new, noninvasive imag-

COMPARISON OF MEASUREMENTS

Methods Being Compared	A-P		R-L		FL		TS	
	ICC	p	ICC	p	ICC	p	ICC	p
Endoscopy vs pathology	.79	.0001	.53	.0062			.45	.0068
Virtual bronchoscopy vs pathology	.42	.010	.52	.0064	.72	.0001	.68	.0002

A-P — anteroposterior, R-L — right-left, FL — full length of stenosis, TS — length of tightest stenosis, ICC — interclass correlation coefficient.

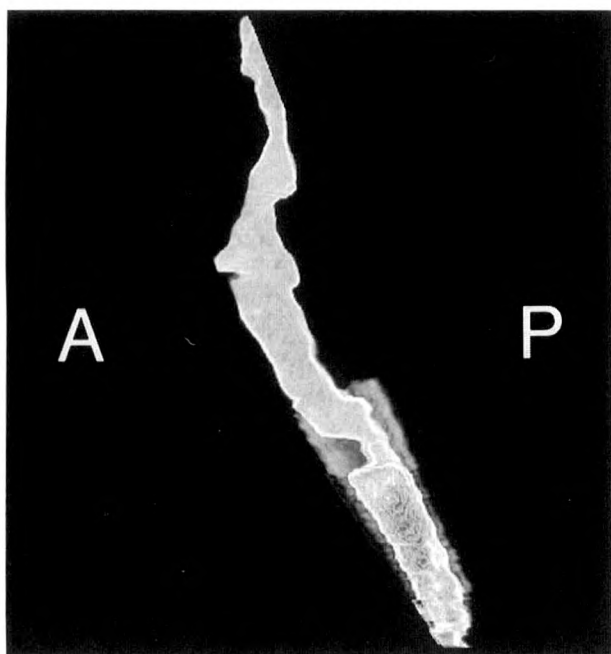


Fig 5. Reconstruction of airway and metallic stent in patient suffering from subglottic and tracheal stenosis. Granulation tissue obstructs anterior two thirds of upper part of stent. A — anterior, P — posterior.

ing technique made possible with spiral CT and advances in computer hardware and software.¹⁻⁴ Compared to a regular CT scan, spiral CT exposes the patient to less radiation,² loses fewer details,⁴ and shows fewer artifacts caused by cardiac motion or differences in the depth of respiration.^{2,3} Many reconstructive visualization techniques have been developed for spiral CT data.^{3,5} They include multiplanar reconstructions, multiplanar volume reconstructions (thickened tomograms), external rendering, and internal rendering. The latter 2 techniques rely upon surface rendering and volume rendering, which show body cavities and hollow structures from the inside.^{1,3,4}

Virtual bronchoscopy offers several advantages over regular endoscopy.

1. Virtual bronchoscopy is better at showing structures (like the trachea or bronchi) that are complex or tortuous.^{1,16}

2. It can show the extent of laryngotracheal neoplasms.⁴

3. It can show the distal parts of laryngotracheal lesions that cannot be reached by a bronchoscope because of proximal airway obstruction. It can also show the airway distal to an obstruction to rule out additional disorders.^{4,10,13,17}

4. It can render simulated airway walls semitransparent, thereby displaying the 3-D relationships between the airway and the surrounding soft tissue. This

ability can be used to guide transtracheal or transbronchial needle aspiration biopsies.^{7,10,13}

Thus, its clinical applications may include medical education, assisting with diagnoses, replacing invasive examinations such as bronchoscopy in selected cases, and helping in planning surgery or endobronchial treatments.^{6,17}

However, VB also has some disadvantages.

1. It is quite expensive, because it requires special equipment and sophisticated image processing. The cost is expected to decrease within the next few years as the technology becomes more widely distributed and the price of computers goes down.^{1,5,7}

2. It is time-consuming.^{3,4}

3. The operator must be experienced in the technique in order to attain optimal results.^{1,3}

4. It is easy to become disoriented, especially during real-time "fly-through" examinations.^{1,8}

5. It cannot show the morphology, vascularity, or color of the mucous membrane, and it cannot detect endoluminal lesions smaller than 2 to 3 mm. Thus, pathological lesions without a space-occupying effect cannot be recognized.^{9,10}

6. Retained secretions and artifacts may result in false-positive findings.^{3,14}

7. There are not yet enough clinical data to judge the accuracy of VB.^{3,5}

Although data are still scarce, preliminary reports of the accuracy of VB are encouraging. Vining et al⁷ compared VB images with videotaped bronchoscopic procedures performed in 20 patients being evaluated for chest problems. In that study, VB reliably demonstrated major airway abnormalities such as airway obstruction and abnormal airway anatomy.

Summers et al⁸ assessed 14 patients with airway abnormalities by VB and found that 90% of bronchi up to the third order could be measured accurately.

Rodenwaldt et al⁹ prospectively evaluated 75 patients with upper airway complaints by VB. All endoluminal space-occupying lesions larger than 5 mm and all stenoses of more than 50% narrowing were correctly detected. The VB measurements of the size and configuration of lesions were identical to endoscopy measurements. Also, VB was able to detect abnormal tracheal anatomy caused by extraluminal compression in all cases.

In a study of the efficacy of VB in 28 patients with stridor and airway obstruction, VB was not as sensitive as endoscopy in detecting airway disease, but it

was more accurate in assessing the width and length of the stenosis.¹¹

The present study was a validation study using specimens, which obviously lack respiratory motion and motion artifact. In this study, endoscopy was better than VB in identifying the A-P diameter of the stenosis. However, the mean difference between VB and the pathological measurements was less than 1 mm. Both VB and endoscopy were equally able to identify the L-R diameter of the stenosis. Both techniques are therefore equivalent in assessing the severity of airway obstruction. On the other hand, endoscopy was not able to evaluate the FL, while VB identified it fairly correctly. Also, VB identified the TS, while endoscopy failed to measure it in 7 of the 18 dogs because of impassable obstructions, and the measurements made by endoscopy were slightly less accurate than the VB ones. We cannot explain why there was a difference in the L-R and A-P measurements by VB, since both are in the imaging plane.

Preoperative knowledge of the FL is helpful in planning reconstructive surgery. It may be crucial in certain situations, such as before tracheal resection with end-to-end anastomosis, when a long tracheal segment is stenosed, and when the surgeon is not convinced that the operation is possible.

Bronchoscopy (flexible or rigid) is still the most accurate method for evaluating the upper airway in

most cases.⁹⁻¹³ However, in patients with upper airway obstruction, bronchoscopy cannot be performed unless the airway is wide enough for the bronchoscope to pass. Also, bronchoscopy sometimes requires general anesthesia. Three-dimensional VB may have a role in certain cases, especially when the structures in question are complex or tortuous, or when endoscopically impassable stenoses, tubes, or stents are encountered. Bronchoscopy and 3-D VB should be considered complementary techniques in these cases, the latter improving the diagnostic approach to these patients. An advantage of VB over regular axial and coronal CT scans is its ability to illustrate complex anatomy in a manner that can be easily comprehended by surgeons who are familiar with the view through a real bronchoscope.^{13,16,21} When patients require LTR or tracheal resection, a noninvasive virtual examination may provide important information to the surgeon, enabling better planning of the extent of the surgery.

CONCLUSIONS

Endoscopy and VB can assess the dimensions of a stenotic laryngeal lumen. Virtual bronchoscopy can better determine the length of the stenosis. Because VB is not invasive and does not require anesthesia, it may be a useful planning tool for certain patients. One possible application is preoperative planning of LTR.

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AGE- AND GENDER-RELATED COLLAGEN DISTRIBUTION IN HUMAN VOCAL FOLDS

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The composition of the lamina propria in human vocal folds has been shown to affect vocal performance. Collagen plays a significant role in the biomechanical effects of the lamina propria. Specifically, it lends tensile strength to the rapidly oscillating fold. We obtained from a state medical examiner 38 larynges from men and women in infant, adult, and geriatric age groups. We stained the vocal folds for collagen using a picric acid stain and studied them using an image analysis system. Distributions of collagen were measured from the superficial to deep layers (from epithelium to vocalis muscle) within the lamina propria. The data showed an increase in collagen content from infant to adult stages. Infant folds had about 51% of the collagen found in all adults and in geriatric patients ($p < .001$). There was no significant difference between adult and geriatric folds ($p < .16$). There was, however, a gender difference in the amount of collagen in both adult and geriatric specimens. Female adult and geriatric folds had about 59% of the collagen found in male adult and geriatric folds ($p < .001$). The distribution pattern of collagen showed that most of the collagen was present in the deep layer. From these data we conclude that there are age-related and gender-related differences between male and female infant, adult, and geriatric vocal folds. Stress-strain performance studies need to be correlated with histologic findings to better study the phonetic implications of these findings.

KEY WORDS — age, collagen, gender, lamina propria, vocal fold.

INTRODUCTION

The lamina propria is a specific tissue layer in human vocal folds that is thought to be of great importance in voice production. It is a trilaminar area immediately deep to the epithelium and superficial to the vocalis muscle, made up of extracellular proteins and a few cells (fibroblasts, myofibroblasts, macrophages).¹ Because of its layered makeup, the histology of the lamina propria is especially important in understanding its role in phonation. A knowledge of this histology would also lead to a better understanding of voice pathology and pathophysiology.

The contribution of the lamina propria and its layered structure to the voice has been explained by many with the cover-body theory of phonation. The theory proposes that the cover (which consists of the epithelium, the superficial layer, and most of the intermediate layer) moves on a relatively stationary body (which includes the remainder of the intermediate layer, the deep layer, and the vocalis muscle).² It is this intricate relationship that allows the vocal fold to vibrate with such consistency and control.

The layers of the lamina propria are defined by their histologic makeup. The most superficial layer

is characterized by a generalized absence of fibrous proteins (collagen and elastin). The intermediate layer generally has higher levels of elastin and some collagen. Finally, the deep layer is defined by an abundant collagen content with some elastin.² The junction of the superficial and intermediate layers is most pronounced histologically.

Studies our group performed to characterize the histologic makeup of the lamina propria have looked at cellularity, proteoglycans, hyaluronic acid, and elastin. Catten et al¹ noted that fibroblasts, myofibroblasts, and macrophages were present, predominantly in the superficial layer. Pawlak et al³ found numerous proteoglycans, including decorin and fibromodulin. Finally, studies by Hammond et al^{4,5} found that men have a higher amount of hyaluronic acid (a shock-absorbing hydrophilic molecule) in the lamina propria than women and that there is an increase in the overall elastin concentration with age from infant to geriatric stages.

Another important protein that is present in the extracellular matrix of the lamina propria but not mentioned in the above studies is collagen. Collagen is an abundant molecule in humans that is important

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because of its high tensile strength. This tensile strength is thought to be a result of the cross-linking present within the molecule.⁶ These cross-links are a result of the covalent bonds between lysine and hydroxylysine residues on adjacent collagen molecules.

Although collagen has been studied extensively throughout the body, including the vocal folds, there have been no computerized quantitative measurements of collagen distribution in the lamina propria with respect to age and gender. We undertook to accomplish this quantitative study with digital image analysis. The hypothesis of this current study is that there are important age-related and gender-related differences in the concentration and distribution of collagen within the lamina propria.

It should be noted that although there are many different types of collagen found throughout the human body, this study did not distinguish among them.

MATERIALS AND METHODS

Larynges were obtained from a state medical examiner within 24 hours of death. No information about the subjects was provided except for age, gender, and race. The subjects were presumed to come from an urban environment because of the geographic area served by the medical examiner. Larynges were examined grossly for injury, and cases in which laryngeal injury was suspected were excluded by the medical examiner. We obtained 21 male and 17 female larynges, including 6 male and 4 female infant larynges (range, 3 to 8 months old), 11 male and 7 female adult larynges (range, 22 to 54 years old), and 4 male and 6 female geriatric larynges (range, 65 to 82 years old). All subjects were white, although race was not a selection factor. One fold from each larynx was extracted en bloc and placed in Carson's fixative for a minimum of 24 hours.

Histologic Staining. The folds were processed routinely with alcoholic dehydration and paraffin embedment. The tissues were embedded to obtain mid-membranous coronal sections of the folds (perpendicular to the vocal ligament). The paraffin blocks were then cut into 4- μ m-thick sections. The sections were stained with picric acid, which stains collagen fibers red. No counterstain was used because of its potential distraction to the imaging process.^{7,8}

Image Analysis. The slides were analyzed with an image analysis system specifically configured for histologic and cytologic studies. The system was run on a Dell Optiplex XMP 5100 Pentium computer (Dallas, Tex) with a 70-MB hard disk. A Microimager 1400 high-resolution (1,280 $\times$ 1,024 $\times$ 10 bit) image scanner (Xillix Tech Corp, Vancouver, Canada) was

mounted on an Olympus BH2 microscope with a DPlanApo 20UV 20 $\times$ lens and a BHT 5 $\times$ photo eyepiece (Olympus Corp, Lake Success, NY). The amount of staining was measured with macro programs developed from Image Pro Plus software (Media Cybernetics) by R. VanBree. This program uses wavelength filters to evaluate tissue structures. Illumination was controlled with a DC Lamp Power Supply (Olympus) that was regulated through the image analysis software.

Optical interference filters were chosen to restrict certain wavelengths of light to maximize contrast within the specimen. For the picric acid stain, a 570-nm filter was used to accentuate the red collagen fibers while deemphasizing other fibrous proteins such as elastin. Proper condenser settings also enhanced contrast. (The settings were checked frequently throughout the imaging process.) The general region of the specimen was found by using the eyepiece of the microscope. The exact location was determined by viewing the specimen directly through the Microimager 1400 on a high-resolution monitor.

The image analysis software uses a gray scale measurement to determine the amount of staining per area measured (stain concentration). After a properly acquired image is obtained, the computer measures the area of the image that is darker than a preset threshold gray scale value. The gray scale value is between 0 and 256, with 0 being black and 256 being white. If the preset threshold is set to 149, then the area of the image that has a value of 149 or lower will be measured as collagen. It is this gray scale measurement that makes the filters and contrast so important for an accurate measurement. (The higher the contrast, the easier the measurement.) If the average value for collagen is 149 or lower and the average value for other fibrous proteins is 220 or higher, the measurements will have much less error than if the average value for collagen is 180 and the average value for the fibrous proteins is 190.

Because the amount of collagen is distributed in a layered pattern throughout the lamina propria, to obtain an accurate representation of the collagen concentration as well as to measure its pattern of distribution, it is necessary to measure an entire strip or swath of lamina propria from the epithelial surface to the vocalis muscle. This was done by taking multiple overlapping fields, beginning with the most superficial field and ending with the fields adjacent to muscular tissue. It should be noted that although the superficial border was well defined, the border adjacent to the muscle often was not. Hence, the deep border was usually set at a point in which the muscular tissue filled more than approximately 25% of

TABLE 1. MEAN COLLAGEN CONCENTRATION

Patient Category	No. of Specimens	Lamina Propria Section					Total
		0-20	20-40	40-60	60-80	80-100	
Infant male	6	3,349	2,833	1,878	1,839	3,622	2,704
Infant female	4	2,821	2,097	1,710	2,228	3,462	2,463
Adult male	11	4,024	3,762	5,232	7,057	8,971	5,809
Adult female	7	4,001	2,950	2,891	4,942	7,300	4,416
Geriatric male	4	4,731	5,983	6,829	8,149	8,369	6,811
Geriatric female	6	2,150	1,485	2,149	3,524	5,881	3,037
Total	38	3,565	3,165	3,582	4,892	6,687	

Data are in arbitrary collagen concentration units, ranging from 0 to 20,000 (0 = field measured contained no collagen, 20,000 = field was completely filled with collagen). Numbered columns represent section of lamina propria measured in percentages (0-20 = most superficial 20% of lamina propria, 80-100 = deepest 20% of lamina propria).

the field. The usual amount of muscular tissue in the deepest field was approximately 10% to 15%. The number of fields necessary to cross the lamina propria varied (up to 20 frames), depending on the thickness of the lamina propria and the angle of the section. (A section cut more diagonally would appear to be thicker and use more frames than the same section cut more perpendicularly.) All of these fields were used in determining the distribution and total amount of collagen present in a given specimen. Multiple strips were taken from each specimen to ensure that a representative measurement was made.

Variation Strategy. Variation was the principal obstacle in making these measurements because of our limited sample size. (We had an average of 6 specimens per category.) To reduce this variation as much as possible, we took several precautions. First, a single observer made all of the measurements. Single-observer reproducibility has been shown to be higher than dual-observer reproducibility (the theory being that if errors are present, the same errors will be present in all specimens, making comparison statistics relatively accurate).⁹ Second, constant checks were done during the measurement process (samples were measured multiple times and results compared) to ensure that the equipment and the observer were obtaining repeatable results. Third, the study was conducted in a blinded and randomized fashion. The slides were imaged in a random order and with the observer blinded to the age and sex of the patient.

Using these precautions, we were able to obtain reproducible data with minimum variation from a limited sample size.

Data Analysis. Once individual measurements were made, we converted the measurements into a comparable form. First, we combined measurements from multiple strips taken from a single specimen to obtain a single representative data set for a given specimen. Then we combined all of these data sets that were in the same category (infant male, geriatric female, etc). Finally, after the category data set was finished, we made comparisons between categories (infant males, geriatric males, etc) for total collagen concentration (Table 1).

A Mann-Whitney test was performed on the data for total collagen content to determine whether the individual categories were different enough to be statistically significant. This test ranks all of the samples from 2 groups (eg, infant male and adult female) as if they were all in 1 large group. It then analyzes the ranks of the cases for statistical difference. The test was performed on all combinations of categories, and all p values are reported as 2-tailed calculations (Table 2).

After making comparisons for total collagen concentration, we analyzed the distribution patterns for each category (Fig 1). Because of the variation in frame number (see Image Analysis, above), it was necessary to normalize all of the field numbers. This

TABLE 2. RESULTS OF MANN-WHITNEY TEST TO DETERMINE CORRELATION BETWEEN GROUPS

	Infant Male	Infant Female	Adult Male	Adult Female	Geriatric Male	Geriatric Female
Infant male		.579	<.001	.022	<.001	.615
Infant female	.579		<.001	.016	<.001	.843
Adult male	<.001	<.001		.032	.250	<.001
Adult female	.022	.016	.032		.003	.020
Geriatric male	<.001	<.001	.250	.003		<.001
Geriatric female	.615	.843	<.001	.020	<.001	

Data are p values.

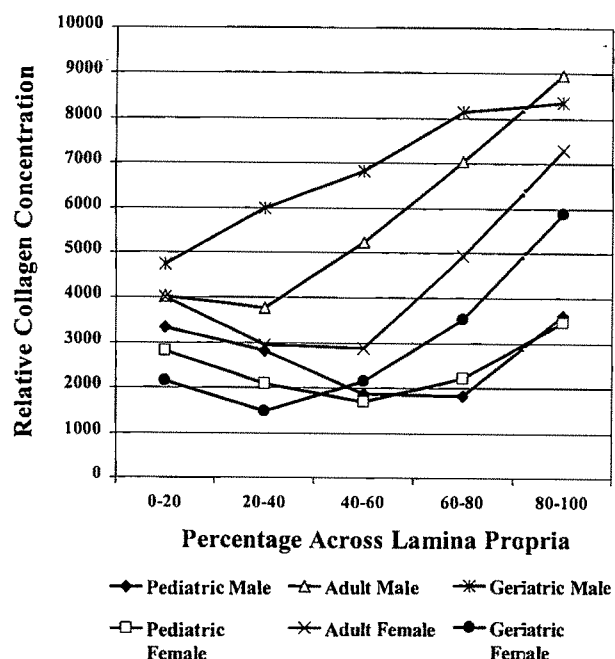


Fig 1. Collagen concentration distribution in human vocal folds. Amounts are in arbitrary collagen concentration units, ranging from 0 to 20,000 (0 — field measured contained no collagen; 20,000 — field was completely filled with collagen).

normalization was done by dividing the field number by the total number of fields for that specimen. This technique was used successfully in previous studies by Catten et al¹ and Hammond et al.⁵ The result was a percentage value assigned to all the field numbers in a given measurement set (swath). The percentile corresponded to the relative depth across the lamina propria (0 being the most superficial and 1 being the deepest). For example, field number 5 in a specimen with 16 total fields would have a normalized field number of 0.31 ($5/16 = 0.31$), meaning that its location was approximately 31% of the distance across the lamina propria in that particular specimen. Field number 5 in a specimen with 11 total fields would have a normalized field number of 0.45 ($5/11 = 0.45$), meaning that its location was approximately 45% of the distance across the lamina propria in that particular specimen.

We then arbitrarily divided the lamina propria into 5 sections for purposes of comparison. Each section represented 20% of the lamina propria. Section 1 was the most superficial section (0% to 20%), and section 5 was the deepest (80% to 100%). We then determined the average amount of collagen staining in that particular section. In the previous example (with 16 frames), all staining measurements from frames 4, 5, and 6 (normalized numbers of 0.25, 0.31, and 0.38, respectively) were added up and divided by 3 to get the average staining per imaged field in the second 20% section of the lamina propria (20% from

the epithelium to 40% from the epithelium). Frames 3 and 7 were not included because their normalized numbers were 0.19 and 0.43, respectively, which lie outside the 20% to 40% range (0.20 to 0.40). The data were organized and analyzed with SPSS Statistical Software Version 7.5 (SPSS Inc, Chicago, Ill).

RESULTS

We found that there was an overall increase in collagen concentration between the infant and adult stages. We also found that gender differences were present in both adult and geriatric specimen groups. We noted overall similarities in the distribution of collagen through the lamina propria, with slight variation with respect to the adult and geriatric male populations. Finally, we found that a consistent band of collagen was present immediately below the epithelium in all specimen groups.

Infants. Infants had the lowest collagen concentration of any of the specimen categories. The collagen concentration was 49.5% of that of adult specimens ($p < .001$) and 57.3% of that of the geriatric specimens ($p < .008$; Table 1 and Fig 2A). The distribution, however, was similar to that of the other categories, in that most of the collagen was present either superficially (immediately deep to the epithelium; Fig 2B) or deep (immediately superficial to the vocalis muscle). The collagen deficiency with respect to the other categories appeared to be in the deep layer rather than the superficial layer. (Infant specimens seemed to have the same superficial collagen concentration as adults and actually had a higher superficial collagen concentration than geriatric women, which caused the comparison of infant to geriatric female collagen concentrations to be statistically not significant; Fig 1 and Table 2.) There were no significant gender differences in the infant specimens.

Adults. Adults had a higher average collagen concentration than infants ($p < .001$). Also, although adult women had significantly more collagen than geriatric women, no significant difference in the collagen concentration between adult and geriatric men was found ($p < .152$). The most apparent difference seen in the adult category was a gender difference (Table 1 and Fig 3). Adult men had an average collagen concentration score of 5,809.2, whereas adult women had a score of 4,416.8 (76.0% of the collagen concentration found in men; $p < .001$). The distribution patterns in both categories were similar, in that most of the collagen appeared in the deeper layers (closer to the vocalis muscle). Men did, however, appear to have a proportionately thicker layer of collagen than women (Fig 1). The increase in collagen that characterizes the beginning of the intermediate layer ap-

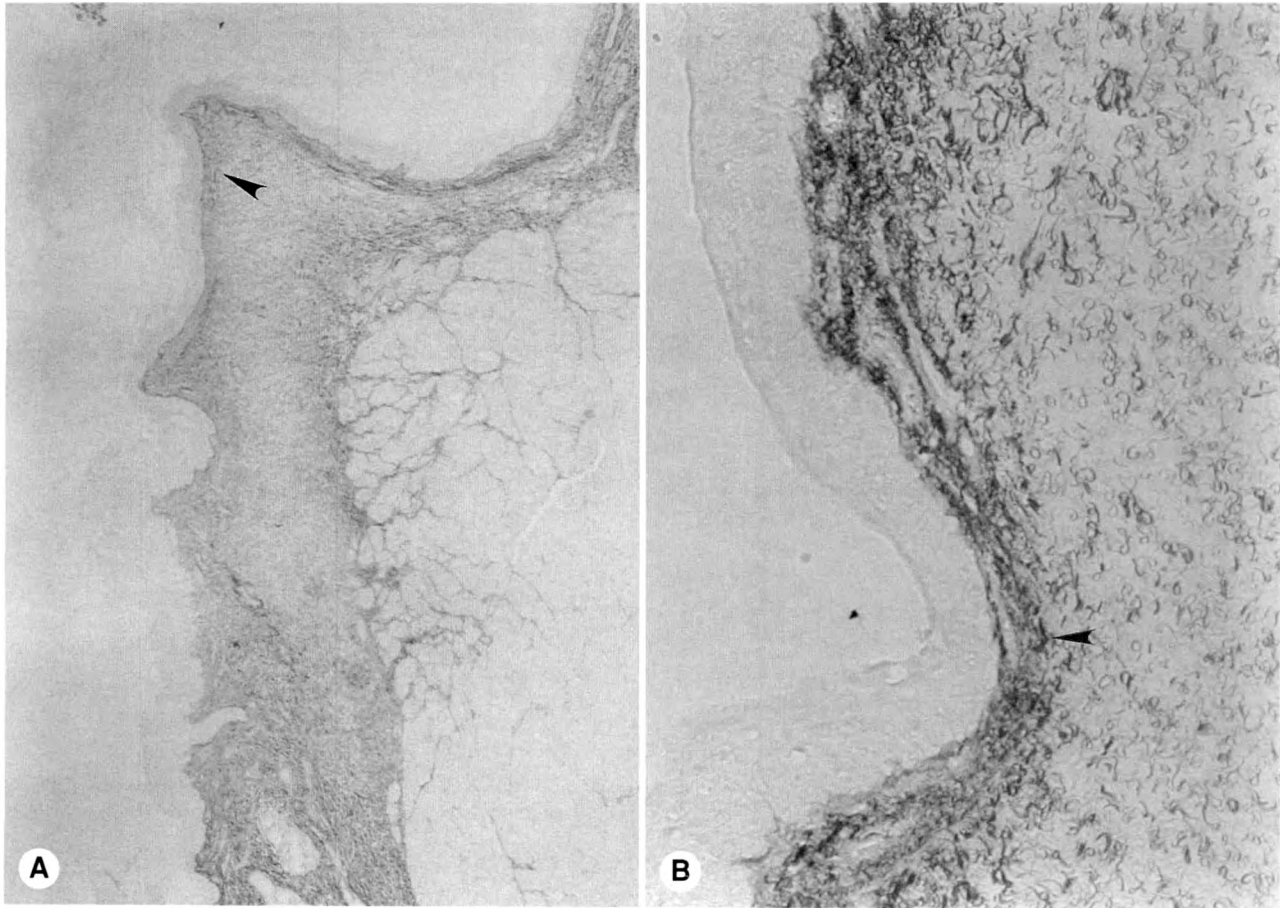


Fig 2. Microscopic photographs of infant human vocal fold. Superficial band of collagen can be seen immediately below epidermis (arrowheads). A) Original $\times 10$. B) Original $\times 20$.

peared to begin at the 20% to 40% range from the epithelium instead of the 40% to 60% range (as it did in women).

Geriatric Subjects. The geriatric specimens were very similar to the adult specimens. Like the adult category, they had a higher average collagen concentration than infants ($p < .008$). There was a significant collagen difference between adult and geriatric women (adults had more than geriatric subjects), but the difference was not significant between adult and geriatric men. The most significant finding was a gender difference ($p < .001$) like that in the adult category, but the difference was even more pronounced (Table 1 and Fig 3). Geriatric men had an average collagen concentration score of 6,811.8, whereas geriatric women had a score of 3,037.2 (44.6% of the collagen concentration found in men). The distribution patterns in both categories were similar, in that most of the collagen appeared in the deeper layers (closer to the vocalis muscle). Geriatric men, like adult men, appeared to have a proportionately thicker layer of collagen than women (Fig 1). The increase in collagen appeared to begin in the 20% to 40% range from the epithelium instead of the 40% to 60%

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DISCUSSION

In this study, it can be seen that there are age- and gender-related changes that occur with respect to collagen. The data show that there is an increase in overall collagen concentration between the infant and adult stages. They also show a gender difference within the adult and geriatric categories, with men generally having a higher collagen concentration than women. The distribution pattern of collagen concentration is similar throughout all categories, but there are marked differences. These differences could be genuine or could be a product of the small sample size of the study.

Collagen has been studied extensively in the context of skin, tendon, and bone aging and disease.¹⁰⁻¹² Research dealing with fibrous proteins in the vocal fold has been somewhat more limited. In looking at the dermatologic research, however, it is noted that changes in collagen do occur with age. For example, collagenous fibers seem to take on an "unraveled" and "fascicular" appearance with age.¹³ Also, it has been noted that both elastin and collagen appear more

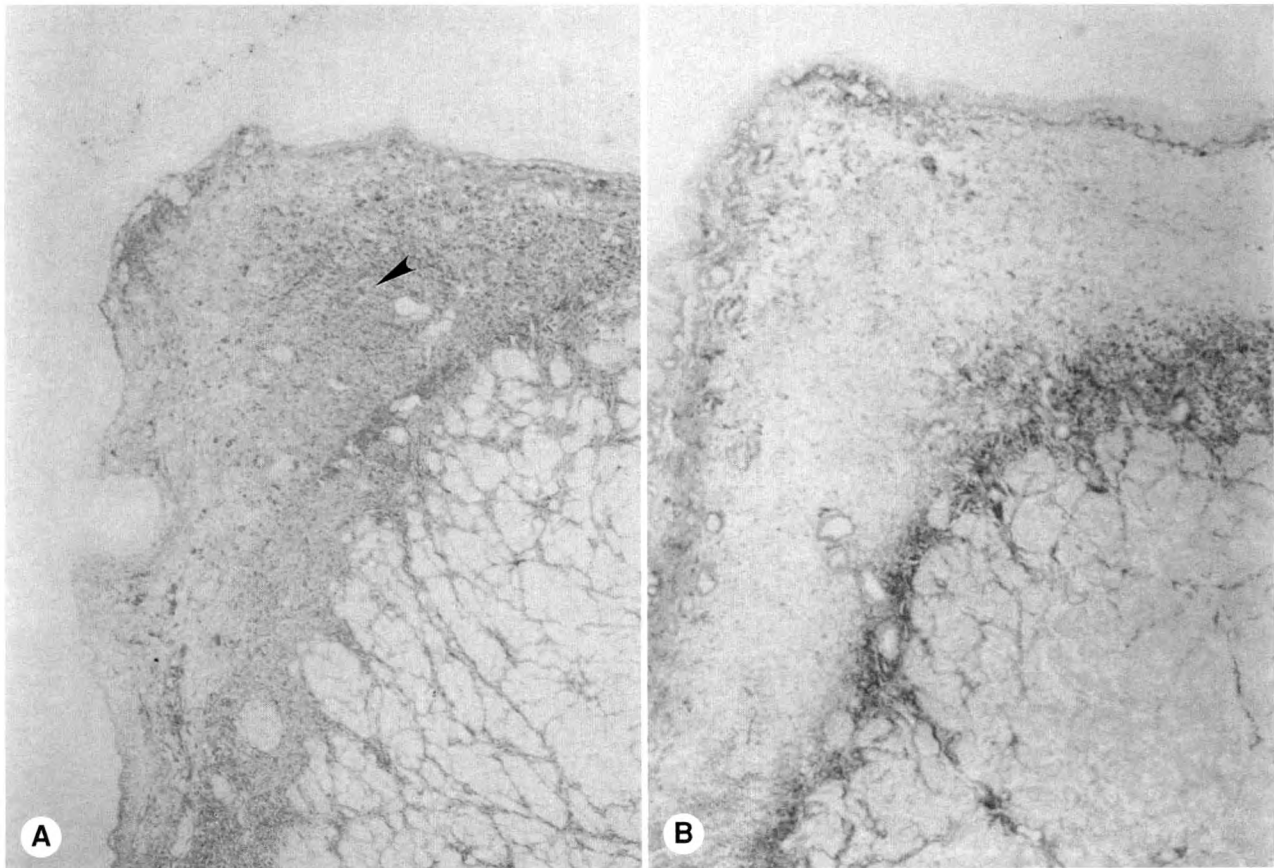


Fig 3. Microscopic photographs of male (A) and female (B) human vocal folds (original $\times 10$). Increased collagen concentration in male fold can be seen in intermediate layer (arrowhead).

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Collagen Concentration. The data suggest that an increase in collagen concentration occurs between the infant and adult stages. This increase seems to slow, stop, or even reverse once adulthood is reached. There also appears to be a gender-related change that occurs between infancy and adulthood. This is manifested by a difference in collagen concentrations between male and female adults that becomes more pronounced in geriatric men and women. (No gender-related difference is readily apparent in infants.)

The reason for a decreased collagen concentration in infants perhaps can be explained by simple vocal fold maturity. Fibrillar proteins develop over time, as do all other substances in the body, and although collagen is present in infant vocal folds, it does not reach substantial proportions until adulthood. In addition, fibrous proteins may be deposited as a result of chronic tissue stress. The lack of fibrillar proteins in infants is supported in the literature through histo-

logic observation.^{2,17,18} The reason for the early occurrence of superficial collagen in infant vocal folds is unknown.

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The gender differences in collagen concentration that appear in the adult and geriatric stages are actually quite large. (Some gender difference is present in infant stages, but this difference is not significant, and the sample size was not large enough for any kind of interpretation.) This is somewhat confusing, because of the presumed relationship of collagen concentration to tension on a given fold. If tension were the only variable responsible for collagen concentration, the observed collagen concentration differences should not exist.

Because the findings of this paper suggest that a

gender difference in collagen density does exist, it is proposed that collagen density cannot be explained solely on the basis of tissue forces. Alternative explanations could include gender-specific biological or environmental factors (hormones, voice use, etc).

Kahane¹⁸ noted this same pattern in men of a change in collagen content. He stated that the change begins about the third decade.¹⁸ He also noted that the increased collagen concentration might be related to the increase in fundamental frequency that occurs in men with age (about the sixth decade).

Collagen Distribution. The distribution of collagen is similar in all age groups. Collagen is present in a superficial band immediately deep to the epithelium (Fig 3), as well as deep in the lamina propria superficial to the vocalis muscle. Although the superficial layer is pronounced in all age groups, the deep layer varies with age and gender.

Most of the age-related variation lies between the infant vocal folds and older, more developed (adult, geriatric) folds. Infant folds have a significantly lower collagen concentration. Surprisingly, almost all of this difference seems to occur in the deep layer, with superficial collagen appearing at a very early stage of life. The reason for the early development of the superficial collagen without concurrent deep collagen development is unknown. (Biomechanical studies to determine the physical contributions of superficial versus deep collagen would greatly aid in determining its significance.) A possible physiological explanation lies in the observation that epithelial cells are capable of collagen secretion.¹⁹ Whereas collagen in the deep layer is secreted by fibroblasts, the overlying epithelium and basement membrane may be responsible for superficial collagen secretion.

It is difficult to comment on the gender differences in collagen distribution in the adult and geriatric age groups. There were noted differences (Table 1 and Fig 1), but it seems premature to draw conclusions from these data because of the limited sample size in

which the differences were noted. The geriatric fold did appear to be a relatively thicker layer of collagen in men than in women in both the adult and geriatric age groups (with collagen occupying a greater percentage of the lamina propria).

Comparison of Collagen With Elastin. In comparing the results of this study with results obtained in a similar study on elastin done 1 year earlier,⁵ it can be noted that both collagen and elastin exhibit age- and gender-related changes. Elastin was found to increase in concentration with age, with no real gender difference, in contrast to collagen. The chronological increase in elastin was thought to be caused by a decrease in elastin turnover rather than an increase in new elastin formation. Collagen concentration was not increased in geriatric subjects. Collagen synthesis may therefore be more evenly balanced throughout adulthood than elastin synthesis and degradation.

The distributions of collagen and elastin also differ in vocal folds (Fig 1). Although both elastin and collagen are sparse in the superficial layer and increase with depth, elastin tends to decrease as it nears the vocalis muscle. Collagen does not show a similar decline. These distributional differences might hint at the differing biomechanics of the intermediate and deep layers. The intermediate layer, with its high elastin content, would exhibit more elasticity, whereas the deep layer, with its abundant collagen, would possess more tensile strength.

CONCLUSION

In conclusion, it has been observed that there are age-related and gender-related differences between male and female infant, adult, and geriatric vocal folds. Adult male and geriatric male folds have significantly more collagen than comparable female folds. Almost all adult and geriatric vocal folds have a higher collagen concentration than infant folds. Stress-strain performance studies need to be correlated with histologic findings to better study the phonetic implications of these findings.

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EFFECTS OF INTRALARYNGEAL CARBON DIOXIDE AND ACETAZOLAMIDE ON THE LARYNGEAL CHEMOREFLEX

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PHILADELPHIA, PENNSYLVANIA

GEORGE S. GODING, JR, MD

MINNEAPOLIS, MINNESOTA

Sudden infant death syndrome is the leading cause of death in infants in the United States. The laryngeal chemoreflex (LCR) is thought to contribute to its pathogenesis. In adult animals, increasing levels of intralaryngeal CO₂ result in a decrease in ventilatory activity. Intravenous acetazolamide (AZ) abolishes this response. The purpose of this study was to determine the effects of intralaryngeal CO₂ and AZ on the LCR and respiratory physiology of piglets under normoxic and hypoxic conditions. We applied 0% or 10% CO₂ in a randomized order to the larynx of 26 piglets. Intubation via tracheotomy prevented inhalation of the gas mixtures. Laryngeal stimulation was performed under normoxic conditions (PaO₂ of >70 mm Hg) in 15 animals and under hypoxic conditions (PaO₂ of 50 to 65 mm Hg) in 11 animals both with and without intravenous AZ (5 mg/kg). Respiratory and cardiovascular response data were recorded. Ten percent intralaryngeal CO₂ has no significant effect on mean baseline respiratory rate, systemic PaCO₂ or PaO₂ levels, or apnea duration ($p > .05$). The use of AZ (versus no AZ) resulted in significantly higher baseline respiratory rates (64 versus 51 breaths per minute; $p = .016$), a decreased baseline systemic PaCO₂ level (38.8 versus 45.9 mm Hg; $p < .001$), a higher baseline PaO₂ level (97.9 versus 82.8 mm Hg; $p < .001$), shorter mean apnea durations (15.5 versus 24.8 seconds; $p = .001$), a higher lowest O₂ saturation level after the stimulus (78.0% versus 68.4%; $p = .003$), and fewer profound apneas (10 of 90 versus 41 of 90 trials; $p < .001$). We conclude that 10% intralaryngeal CO₂ does not decrease ventilatory activity in piglets and has no significant effect on the LCR. Acetazolamide, however, appears to have a protective effect against the LCR, resulting in shorter and less severe apneas. The protective effect of AZ against the LCR appears to be related to its ability to stimulate the respiratory drive and increase oxygenation at baseline.

KEY WORDS — acetazolamide, apnea, carbon dioxide, infant, laryngeal chemoreflex, sudden infant death.

INTRODUCTION

Sudden infant death syndrome is the leading cause of postnatal death in the United States today.¹ The laryngeal chemoreflex (LCR) has been suggested as a possible factor in the pathogenesis of sudden infant death syndrome. Chemical stimulation of the pharynx of infants elicits a reflexive apnea, hypotension, bradycardia, and laryngeal adduction.²⁻⁵ A similar response (the LCR) has been seen with the stimulation of the surgically isolated larynx of young animals.⁶⁻¹⁰ The afferent limb of the LCR is mediated via the superior laryngeal nerve.^{11,12} The severity of the LCR changes as a function of age, increasing during the first weeks of life and subsequently declining over the next several months.^{7,10} Severe or fatal LCR responses are seen only in the very young and have been shown to be present in a variety of species.^{7,13-17} There are several physiological conditions that have been shown to affect the LCR. When the animal is hypoxic at the time of laryngeal stimulation, the response is either a transient, shorter apnea or a profound and potentially fatal apnea with a great-

er degree of hypotension.¹⁸⁻²⁰ Despite longer apneas, if the PaO₂ level is sufficiently high at the time of laryngeal stimulation, blood pressure and coordinated laryngeal responses can be maintained, and the animals are more likely to recover from the apneic response.¹⁸

Studies investigating the effects of the application of carbon dioxide (CO₂) to the larynx of adult animals have suggested the presence of CO₂-sensitive laryngeal chemoreceptors.²¹⁻²⁸ The introduction of 3% to 10% CO₂ into the surgically isolated upper airway of adult animals while systemic PaCO₂ is held constant results in decreased ventilatory activity and in stimulation of the pharyngeal dilators.²¹⁻²⁸ That this response is abolished by sectioning the superior laryngeal nerve suggests that superior laryngeal nerve afferents are sensitive to CO₂.

The application of 10% CO₂ to the larynx of adult cats results in the excitation of quiescent neurons in the superior laryngeal nerve.²² This superior laryngeal nerve response is attenuated by intravenous ad-

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Presented at the meeting of the American Laryngological Association, Palm Desert, California, April 24-25, 1999.

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ministration of the carbonic anhydrase inhibitor acetazolamide (AZ).²⁹ Carbonic anhydrase catalyzes the conversion of CO₂ to bicarbonate (HCO₃⁻) and water, as well as the reverse reaction in many tissues throughout the body. The catalysis of this reaction is inhibited by AZ. The ability of AZ to block the effect of intralaryngeal CO₂ on superior laryngeal nerve activity and ventilation suggests that carbonic anhydrase plays an important role in the detection of transient changes in CO₂ by CO₂-sensitive laryngeal receptors.

If the same laryngeal CO₂ receptors exist in piglets as have been demonstrated in adult animals, then the application of CO₂ to the larynx of piglets should similarly depress ventilatory activity and augment the LCR-induced apneic response, thus leading to more profound apneas. Likewise, the administration of intravenous AZ should inhibit the effects of intralaryngeal CO₂ on the LCR. Acetazolamide has been shown to increase the respiratory drive at high altitudes and in patients with obstructive sleep apnea; the effects of AZ on the LCR are unknown.³⁰⁻³⁵ The goal of this study is to investigate the effects of 10% intralaryngeal CO₂ and AZ on the apneic response to laryngeal chemical stimulation under normoxic conditions. In a second part, the effects of 10% intralaryngeal CO₂ and AZ are examined under hypoxic conditions.

METHODS

Subjects. Twenty-six piglets 13 to 18 days old served as subjects in this study. Fifteen participated in part 1 of the study, and 11 participated in part 2. Piglets in this age group were chosen because they have been shown to reliably produce the LCR in response to laryngeal chemostimulation with water.¹⁸⁻²⁰ All procedures were performed in accordance with the guidelines for the humane treatment of animals at Hennepin County Medical Center.

Surgical Preparation. The piglets were anesthetized with an intramuscular injection of ketamine hydrochloride (40 mg/kg) and xylazine hydrochloride (5 mg/kg) to obtain an initial level of sedation. A continuous intravenous drip of ketamine hydrochloride (1 mg/mL) and xylazine hydrochloride (0.15 mg/mL) was run at a rate of 1 mL/min and titrated as needed to maintain level 3 anesthesia throughout the experiment. Level 3 anesthesia was defined as spontaneous respirations with an absence of a pain reflex. Normal saline solution was given intravenously as a 100-mL bolus at the start of the procedure and subsequently as a drip to maintain blood pressure greater than 90/60 mm Hg and urine output greater than 20 mL/kg per hour throughout the procedure.

Bilateral femoral arterial lines were placed. One

arterial line was used for blood pressure monitoring, and the other was used for arterial blood gas sampling. The rectal temperature was monitored via a temperature probe and maintained between 36.0°C and 40.0°C with a heating pad. The peripheral blood oxygen saturation level and pulse were monitored with a pulse oximeter (Nellcor, Hayward, Calif) secured on the snout. Platinum subdermal electrodes (Grass Instruments, Inc, Quincy, Mass, model E2) were placed on the abdomen and connected to monitors (Hewlett-Packard Co, Medical Products Group, Andover, Mass, models 78202B and 78203C) and an oscilloscope (Hewlett-Packard, model 78303B) to monitor respiration.

A vertical midline neck incision was made to expose the larynx and trachea. A low cervical tracheotomy was performed by making a vertical incision through the third, fourth, and fifth tracheal rings. An appropriately sized cuffed endotracheal tube was placed through the tracheotomy, and the cuff was inflated to a low pressure level. A Giebeck Humid-Vent Mini (Giebeck Respiration, Upplands Vasby, Sweden) was placed at the end of the endotracheal tube to help prevent loss of moisture and heat with ventilation. A Nellcor N-1000 apnea monitor was attached to the end of the endotracheal tube to monitor the end-tidal CO₂ level. The animals were allowed to breathe room air through the endotracheal tube, which was secured caudally to prevent inhalation of the laryngeal gas mixtures.

A vertical midline thyrotomy was subsequently performed with stay sutures placed to expose the laryngeal mucosa. Platinum subdermal electrode pairs were placed unilaterally in the thyroarytenoid muscle and in the contralateral posterior cricoarytenoid muscle. The electrodes were connected to alternating current preamplifiers (Grass Instruments, p-5 series), and laryngeal muscle activity was monitored on the model 78303B Hewlett-Packard oscilloscope.

A plastic dome was placed over the exposed larynx, through which warmed, humidified air (0% CO₂, 21% O₂) or 10% CO₂ (21% O₂) was blown over the laryngeal mucosa with an Aquatherm III nebulizer heater (Hudson RCI, Temecula, Calif). A Perfusion Flowmeter System gas mixer (CR Bard, Inc, Santa Ana, Calif, model H410) was used to mix the CO₂ with O₂ and compressed air. The concentrations of CO₂ and O₂ at the level of the laryngeal mucosa were verified with a Forregger CO₂ monitor (Datex Instrumentarium OI, Helsinki, Finland) and an oxygen monitor (Hudson RCI), respectively. The caudally positioned tracheotomy tube ensured isolation of the laryngeal gas mixtures from the pulmonary and systemic circulation.

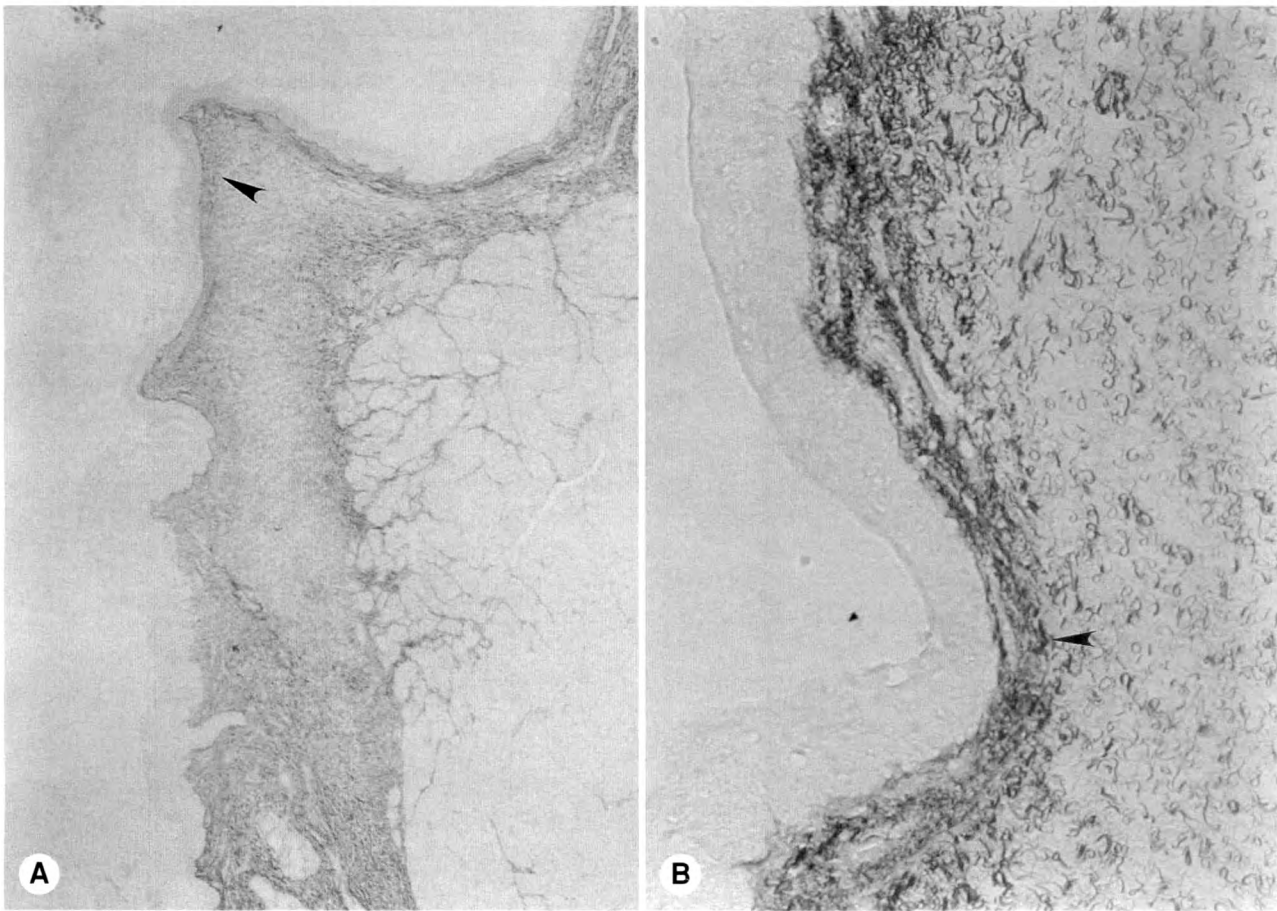


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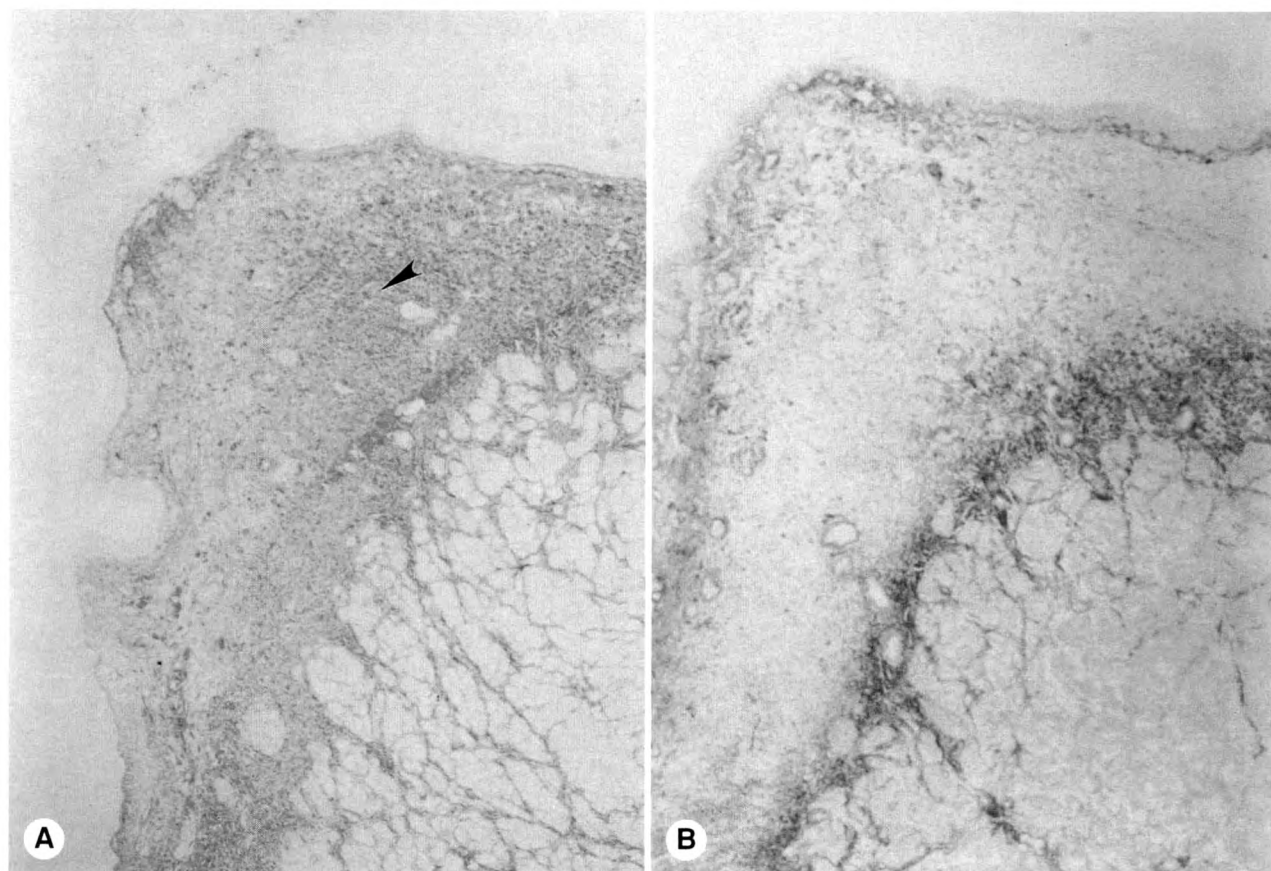


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Kahane¹⁸ noted this same pattern in men of a change in collagen content. He stated that the change begins about the third decade.¹⁸ He also noted that the increased collagen concentration might be related to the increase in fundamental frequency that occurs in men with age (about the sixth decade).

Collagen Distribution. The distribution of collagen is similar in all age groups. Collagen is present in a superficial band immediately deep to the epithelium (Fig 3), as well as deep in the lamina propria superficial to the vocalis muscle. Although the superficial layer is pronounced in all age groups, the deep layer varies with age and gender.

Most of the age-related variation lies between the infant vocal folds and older, more developed (adult, geriatric) folds. Infant folds have a significantly lower collagen concentration. Surprisingly, almost all of this difference seems to occur in the deep layer, with superficial collagen appearing at a very early stage of life. The reason for the early development of the superficial collagen without concurrent deep collagen development is unknown. (Biomechanical studies to determine the physical contributions of superficial versus deep collagen would greatly aid in determining its significance.) A possible physiological explanation lies in the observation that epithelial cells are capable of collagen secretion.¹⁹ Whereas collagen in the deep layer is secreted by fibroblasts, the overlying epithelium and basement membrane may be responsible for superficial collagen secretion.

It is difficult to comment on the gender differences in collagen distribution in the adult and geriatric age groups. There were noted differences (Table 1 and Fig 1), but it seems premature to draw conclusions from these data because of the limited sample size in

which the differences were shown. That said, there did appear to be a relatively thicker collagenous layer in men than in women in both the adult and geriatric age groups (with collagen occupying a greater percentage of the lamina propria).

Comparison of Collagen With Elastin. In comparing the results of this study with results obtained in a similar study on elastin done 1 year earlier,⁵ it can be noted that both collagen and elastin exhibit age- and gender-related changes. Elastin was found to increase in concentration with age, with no real gender difference, in contrast to collagen. The chronological increase in elastin was thought to be caused by a decrease in elastin turnover rather than an increase in new elastin formation. Collagen concentration was not increased in geriatric subjects. Collagen synthesis may therefore be more evenly balanced throughout adulthood than elastin synthesis and degradation.

The distributions of collagen and elastin also differ in vocal folds (Fig 1). Although both elastin and collagen are sparse in the superficial layer and increase with depth, elastin tends to decrease as it nears the vocalis muscle. Collagen does not show a similar decline. These distributional differences might hint at the differing biomechanics of the intermediate and deep layers. The intermediate layer, with its high elastin content, would exhibit more elasticity, whereas the deep layer, with its abundant collagen, would possess more tensile strength.

CONCLUSION

In conclusion, it has been observed that there are age-related and gender-related differences between male and female infant, adult, and geriatric vocal folds. Adult male and geriatric male folds have significantly more collagen than comparable female folds. Almost all adult and geriatric vocal folds have a higher collagen concentration than infant folds. Stress-strain performance studies need to be correlated with histologic findings to better study the phonetic implications of these findings.

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EFFECTS OF INTRALARYNGEAL CARBON DIOXIDE AND ACETAZOLAMIDE ON THE LARYNGEAL CHEMOREFLEX

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Sudden infant death syndrome is the leading cause of death in infants in the United States. The laryngeal chemoreflex (LCR) is thought to contribute to its pathogenesis. In adult animals, increasing levels of intralaryngeal CO₂ result in a decrease in ventilatory activity. Intravenous acetazolamide (AZ) abolishes this response. The purpose of this study was to determine the effects of intralaryngeal CO₂ and AZ on the LCR and respiratory physiology of piglets under normoxic and hypoxic conditions. We applied 0% or 10% CO₂ in a randomized order to the larynx of 26 piglets. Intubation via tracheotomy prevented inhalation of the gas mixtures. Laryngeal stimulation was performed under normoxic conditions (PaO₂ of >70 mm Hg) in 15 animals and under hypoxic conditions (PaO₂ of 50 to 65 mm Hg) in 11 animals both with and without intravenous AZ (5 mg/kg). Respiratory and cardiovascular response data were recorded. Ten percent intralaryngeal CO₂ has no significant effect on mean baseline respiratory rate, systemic PaCO₂ or PaO₂ levels, or apnea duration ($p > .05$). The use of AZ (versus no AZ) resulted in significantly higher baseline respiratory rates (64 versus 51 breaths per minute; $p = .016$), a decreased baseline systemic PaCO₂ level (38.8 versus 45.9 mm Hg; $p < .001$), a higher baseline PaO₂ level (97.9 versus 82.8 mm Hg; $p < .001$), shorter mean apnea durations (15.5 versus 24.8 seconds; $p = .001$), a higher lowest O₂ saturation level after the stimulus (78.0% versus 68.4%; $p = .003$), and fewer profound apneas (10 of 90 versus 41 of 90 trials; $p < .001$). We conclude that 10% intralaryngeal CO₂ does not decrease ventilatory activity in piglets and has no significant effect on the LCR. Acetazolamide, however, appears to have a protective effect against the LCR, resulting in shorter and less severe apneas. The protective effect of AZ against the LCR appears to be related to its ability to stimulate the respiratory drive and increase oxygenation at baseline.

KEY WORDS — acetazolamide, apnea, carbon dioxide, infant, laryngeal chemoreflex, sudden infant death.

INTRODUCTION

Sudden infant death syndrome is the leading cause of postnatal death in the United States today.¹ The laryngeal chemoreflex (LCR) has been suggested as a possible factor in the pathogenesis of sudden infant death syndrome. Chemical stimulation of the pharynx of infants elicits a reflexive apnea, hypotension, bradycardia, and laryngeal adduction.²⁻⁵ A similar response (the LCR) has been seen with the stimulation of the surgically isolated larynx of young animals.⁶⁻¹⁰ The afferent limb of the LCR is mediated via the superior laryngeal nerve.^{11,12} The severity of the LCR changes as a function of age, increasing during the first weeks of life and subsequently declining over the next several months.^{7,10} Severe or fatal LCR responses are seen only in the very young and have been shown to be present in a variety of species.^{7,13-17} There are several physiological conditions that have been shown to affect the LCR. When the animal is hypoxic at the time of laryngeal stimulation, the response is either a transient, shorter apnea or a profound and potentially fatal apnea with a great-

er degree of hypotension.¹⁸⁻²⁰ Despite longer apneas, if the PaO₂ level is sufficiently high at the time of laryngeal stimulation, blood pressure and coordinated laryngeal responses can be maintained, and the animals are more likely to recover from the apneic response.¹⁸

Studies investigating the effects of the application of carbon dioxide (CO₂) to the larynx of adult animals have suggested the presence of CO₂-sensitive laryngeal chemoreceptors.²¹⁻²⁸ The introduction of 3% to 10% CO₂ into the surgically isolated upper airway of adult animals while systemic PaCO₂ is held constant results in decreased ventilatory activity and in stimulation of the pharyngeal dilators.²¹⁻²⁸ That this response is abolished by sectioning the superior laryngeal nerve suggests that superior laryngeal nerve afferents are sensitive to CO₂.

The application of 10% CO₂ to the larynx of adult cats results in the excitation of quiescent neurons in the superior laryngeal nerve.²² This superior laryngeal nerve response is attenuated by intravenous ad-

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ministration of the carbonic anhydrase inhibitor acetazolamide (AZ).²⁹ Carbonic anhydrase catalyzes the conversion of CO₂ to bicarbonate (HCO₃⁻) and water, as well as the reverse reaction in many tissues throughout the body. The catalysis of this reaction is inhibited by AZ. The ability of AZ to block the effect of intralaryngeal CO₂ on superior laryngeal nerve activity and ventilation suggests that carbonic anhydrase plays an important role in the detection of transient changes in CO₂ by CO₂-sensitive laryngeal receptors.

If the same laryngeal CO₂ receptors exist in piglets as have been demonstrated in adult animals, then the application of CO₂ to the larynx of piglets should similarly depress ventilatory activity and augment the LCR-induced apneic response, thus leading to more profound apneas. Likewise, the administration of intravenous AZ should inhibit the effects of intralaryngeal CO₂ on the LCR. Acetazolamide has been shown to increase the respiratory drive at high altitudes and in patients with obstructive sleep apnea; the effects of AZ on the LCR are unknown.³⁰⁻³⁵ The goal of this study is to investigate the effects of 10% intralaryngeal CO₂ and AZ on the apneic response to laryngeal chemical stimulation under normoxic conditions. In a second part, the effects of 10% intralaryngeal CO₂ and AZ are examined under hypoxic conditions.

METHODS

Subjects. Twenty-six piglets 13 to 18 days old served as subjects in this study. Fifteen participated in part 1 of the study, and 11 participated in part 2. Piglets in this age group were chosen because they have been shown to reliably produce the LCR in response to laryngeal chemostimulation with water.¹⁸⁻²⁰ All procedures were performed in accordance with the guidelines for the humane treatment of animals at Hennepin County Medical Center.

Surgical Preparation. The piglets were anesthetized with an intramuscular injection of ketamine hydrochloride (40 mg/kg) and xylazine hydrochloride (5 mg/kg) to obtain an initial level of sedation. A continuous intravenous drip of ketamine hydrochloride (1 mg/mL) and xylazine hydrochloride (0.15 mg/mL) was run at a rate of 1 mL/min and titrated as needed to maintain level 3 anesthesia throughout the experiment. Level 3 anesthesia was defined as spontaneous respirations with an absence of a pain reflex. Normal saline solution was given intravenously as a 100-mL bolus at the start of the procedure and subsequently as a drip to maintain blood pressure greater than 90/60 mm Hg and urine output greater than 20 mL/kg per hour throughout the procedure.

Bilateral femoral arterial lines were placed. One

arterial line was used for blood pressure monitoring, and the other was used for arterial blood gas sampling. The rectal temperature was monitored via a temperature probe and maintained between 36.0°C and 40.0°C with a heating pad. The peripheral blood oxygen saturation level and pulse were monitored with a pulse oximeter (Nellcor, Hayward, Calif) secured on the snout. Platinum subdermal electrodes (Grass Instruments, Inc, Quincy, Mass, model E2) were placed on the abdomen and connected to monitors (Hewlett-Packard Co, Medical Products Group, Andover, Mass, models 78202B and 78203C) and an oscilloscope (Hewlett-Packard, model 78303B) to monitor respiration.

A vertical midline neck incision was made to expose the larynx and trachea. A low cervical tracheotomy was performed by making a vertical incision through the third, fourth, and fifth tracheal rings. An appropriately sized cuffed endotracheal tube was placed through the tracheotomy, and the cuff was inflated to a low pressure level. A Giebeck Humid-Vent Mini (Giebeck Respiration, Upplands Vasby, Sweden) was placed at the end of the endotracheal tube to help prevent loss of moisture and heat with ventilation. A Nellcor N-1000 apnea monitor was attached to the end of the endotracheal tube to monitor the end-tidal CO₂ level. The animals were allowed to breathe room air through the endotracheal tube, which was secured caudally to prevent inhalation of the laryngeal gas mixtures.

A vertical midline thyrotomy was subsequently performed with stay sutures placed to expose the laryngeal mucosa. Platinum subdermal electrode pairs were placed unilaterally in the thyroarytenoid muscle and in the contralateral posterior cricoarytenoid muscle. The electrodes were connected to alternating current preamplifiers (Grass Instruments, p-5 series), and laryngeal muscle activity was monitored on the model 78303B Hewlett-Packard oscilloscope.

A plastic dome was placed over the exposed larynx, through which warmed, humidified air (0% CO₂, 21% O₂) or 10% CO₂ (21% O₂) was blown over the laryngeal mucosa with an Aquatherm III nebulizer heater (Hudson RCI, Temecula, Calif). A Perfusion Flowmeter System gas mixer (CR Bard, Inc, Santa Ana, Calif, model H410) was used to mix the CO₂ with O₂ and compressed air. The concentrations of CO₂ and O₂ at the level of the laryngeal mucosa were verified with a Forregger CO₂ monitor (Datex Instrumentarium OI, Helsinki, Finland) and an oxygen monitor (Hudson RCI), respectively. The caudally positioned tracheotomy tube ensured isolation of the laryngeal gas mixtures from the pulmonary and systemic circulation.

Physiological Conditions and Experimental Protocol: Part 1. Laryngeal stimulation was performed under normoxic conditions (PaO₂ of >70 mm Hg) in each trial. All animals underwent laryngeal stimulation 3 times with 0% CO₂ and 3 times with 10% CO₂, presented in a randomized order. End-tidal CO₂ monitoring and arterial blood gas analysis were performed before and after each application of the gas mixtures over the larynx to ensure that the systemic PaCO₂ level was not altered by the application of 0% or 10% CO₂ over the larynx.

The following baseline physiological data were recorded before each stimulation: rectal temperature, respiratory rate, arterial blood pressure, pulse, O₂ saturation, end-tidal CO₂, and arterial blood gas data (pH, PaCO₂, PaO₂, and calculated HCO₃⁻). The gas mixture (0% or 10% CO₂) was blown over the larynx. After a period of 2 minutes of laryngeal exposure to the mixture, the above physiological data were again recorded.

Distilled water (5 mL) titrated to a pH of 3 with 1-mol/L hydrochloric acid was applied to the laryngeal mucosa to elicit the LCR. Respirations, arterial blood pressure, O₂ saturation level, end-tidal CO₂ level, and muscle electromyographic activity of the thyroarytenoid and posterior cricoarytenoid muscles were monitored and recorded in a computer-assisted data storage and analysis system (Labview 4.1 Graphical Programming for Instrumentation, National Instruments, Austin, Tex). At the moment the animal took its first breath after the apnea, arterial blood gas analysis was again performed, and the O₂ saturation level, arterial blood pressure, pulse, and end-tidal CO₂ level were again recorded. The values of the O₂ saturation level, arterial blood pressure, and end-tidal CO₂ level at the first breath were confirmed with review of the recorded data on Labview.

The animals were observed for 4 minutes after laryngeal stimulation. Those animals that had resumed respirations but whose O₂ saturation level did not exceed 90% at the end of this 4-minute period were given supplemental O₂ delivered via blow-by at a rate of 2 L/min. Animals that did not resume respirations after 90 seconds of apnea or whose O₂ saturation level did not exceed 90% with supplemental O₂ were given positive pressure ventilation until they resumed a respiratory pattern that enabled them to maintain their O₂ saturation levels above 90% with 2 L/min of blow-by O₂. Criteria for proceeding to the next experimental trial included a blood pressure greater than 90/60 mm Hg, a pulse greater than 60 beats per second, and an O₂ saturation level greater than 90%. Animals that failed to meet these criteria were given supplemental O₂ or normal saline solu-

tion boluses as needed to achieve these values. The animals were allowed a 10-minute minimum recovery period at the target blood pressure, pulse, and O₂ saturation level before the start of the next trial.

After the animals had undergone 3 trials in each condition (0% or 10% CO₂), AZ (5 mg/kg) was injected intravenously. After a period of 10 minutes, the animals again randomly underwent stimulation 3 times in each condition (0% or 10% CO₂). Laryngeal stimulation was again performed under normoxic conditions (PaO₂ of >70 mm Hg) during all trials, and data were collected in a similar manner.

Physiological Conditions and Experimental Protocol: Part 2. All animals underwent initial stimulation under normoxic conditions, with 0% CO₂ blown over the larynx. The protocol for this physiological condition was identical to the protocol used in part 1 of the study for the 0% CO₂ experimental group.

For the hypoxic trials, 10% or 0% CO₂ was blown over the surgically isolated larynx as in part 1. Hypoxia was induced by blowing nitrogen (N₂) by the open end of the tracheotomy tube. The amount of N₂ used was titrated to produce a systemic PaO₂ of 50 to 65 mm Hg. The piglets were allowed to remain hypoxic for 3 minutes. They then underwent laryngeal stimulation once under each condition (0% or 10% CO₂) in a randomized order. Subsequently, AZ (5 mg/kg) was injected intravenously. After a period of 10 minutes, hypoxia was again induced with N₂, and the animals randomly underwent stimulation while hypoxic, once each with 0% and 10% intralaryngeal CO₂.

The animals' response to laryngeal stimulation was observed. After the apneic response, animals that resumed respirations but whose O₂ saturation level did not exceed 80% after 1 minute of recovery were given supplemental O₂ (2 L/min blow-by). Those animals that met this milestone but whose O₂ saturation level did not exceed 85% after 1.5 minutes were also given supplemental O₂ (2 L/min blow-by), as were piglets whose O₂ saturation level was less than 90% 2 minutes after recovery. Piglets that had an apneic response that lasted longer than 60 seconds or whose O₂ saturation level did not exceed 90% with supplemental O₂ were given positive pressure ventilation until they resumed a respiratory pattern that enabled them to maintain their O₂ saturation level above 90% with 2 L/min of blow-by O₂. These criteria were used to prevent ischemic damage to the respiratory centers in the brain stem.

The animals were allowed a minimum 10-minute recovery period before the start of the next trial. During the first 7 minutes of this recovery period, all

TABLE 1. PART 1: MEAN PRESTIMULATION RESPIRATORY MEASURES (NORMOXIA; N = 15)

	Respiratory Rate (breaths/min)		PaCO ₂ (mm Hg)		PaO ₂ (mm Hg)		pH	
	0% CO ₂	10% CO ₂	0% CO ₂	10% CO ₂	0% CO ₂	10% CO ₂	0% CO ₂	10% CO ₂
Without AZ	50.7 ± 17.6	51.6 ± 15.8	45.9 ± 4.9	45.6 ± 4.4	82.8 ± 4.5	83.4 ± 4.2	7.34 ± 0.051	7.34 ± 0.055
With AZ	64.2 ± 15.4	62.9 ± 13.5	38.8 ± 4.0	39.7 ± 4.3	97.9 ± 8.9	98.6 ± 9.4	7.35 ± 0.053	7.34 ± 0.064
p (AZ vs no AZ)	.01	.03	<.001	<.001	<.001	<.001	>.05	>.05

p values for 0% CO₂ versus 10% CO₂ with and without AZ are >.05 for all variables (paired samples *t*-test).
AZ — acetazolamide.

animals were given supplemental blow-by O₂ (2 L/min) to minimize respiratory effort during recovery. Criteria for proceeding to the next experimental trial were the same as in part 1. After collection of physiological data, euthanasia and postmortem examination were performed as in part 1.

Data Analysis. The data were analyzed from the digital record. Respiratory rate, O₂ saturation level, apnea duration, and arterial blood gas analysis from each of the 3 trials in each experimental condition in part 1 of the study (0% CO₂, 10% CO₂, 0% CO₂ with AZ, or 10% CO₂ with AZ) were averaged and represented a single data point for each animal for that experimental condition. The raw data for each experimental condition in part 2 of the study (hypoxic stimulation with 0% CO₂, 10% CO₂, 0% CO₂ with AZ, or 10% CO₂ with AZ, or normoxic stimulation with 0% CO₂) was used as a single data point for each animal for analysis of part 2. The apneic response to laryngeal stimulation was analyzed by measuring the time between the last respiration before stimulation and the first recovery breath. The first recovery breath was defined as the first breath after

laryngeal stimulation that was followed by a second breath within the next 5 seconds. Paired samples *t*-tests were used to compare the results of each experimental condition in the analysis of each variable except the ability to recover.

Ability to recover was categorized as without assistance (mild apnea), with O₂ (moderate apnea), or with positive pressure ventilation (profound apnea) as described above. Because recovery represents categorical data, each trial in each experimental condition (3 trials per condition times 15 animals in part 1 and 1 trial per condition times 11 animals in part 2) served as a single data point in both part 1 and part 2 of the study. These data was analyzed with the Wilcoxon signed ranks test. The ability to recover without assistance was assigned a rank of 0, recovery with O₂ was assigned a rank of 1, and recovery with positive pressure ventilation was assigned a rank of 2. The designated level for α was .05 for all statistical tests.

RESULTS

Part 1. All piglets survived the experimental trials with a normal respiratory pattern and blood pressure after recovery from LCR stimulation. Pulmonary aspiration of the stimulating solution did not occur. All animals responded to laryngeal stimulation with a pause in respiration. Postmortem examination revealed that the posterior cricoarytenoid and thyroarytenoid electrodes were in the appropriate muscles and that the tracheotomy tube was placed at least 4 cm above the carina in all animals.

Injection of AZ resulted in an increase in respiratory rate, an increase in PaO₂, a decrease in PaCO₂, and no change in pH at baseline (paired samples *t*-test, $p < .05$, $p < .001$, $p < .001$, and $p > .05$, respectively; Table 1). Administration of 10% intralaryngeal CO₂ had no effect on these baseline respiratory measures (paired samples *t*-test, $p > .05$ for each; Table 1).

Administration of 10% CO₂ did not affect the mean apnea duration (paired samples *t*-test, $p > .05$); intravenous AZ shortened the mean apnea duration (paired samples *t*-test, $p = .01$; Fig 1). Similarly, there was

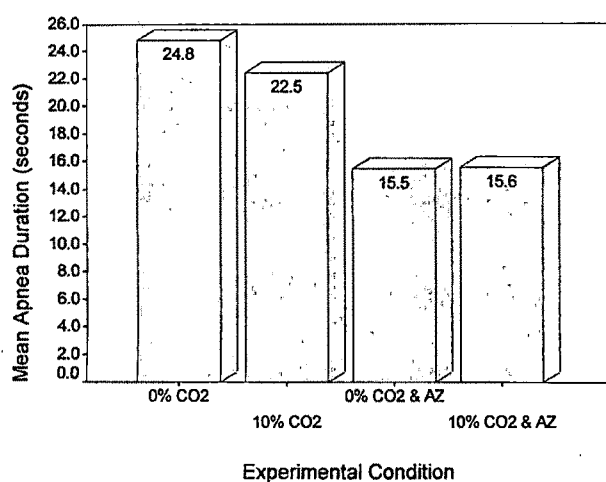
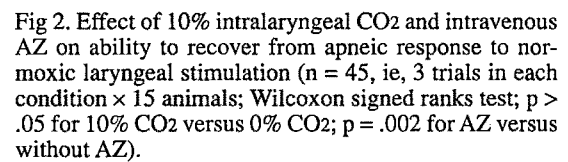


Fig 1. Effect of 10% intralaryngeal CO₂ and intravenous acetazolamide (AZ) on mean apnea duration after normoxic laryngeal stimulation (PaO₂ of >70 mm Hg; n = 15). Standard deviations were 14.1 for 0% CO₂, 15.1 for 10% CO₂, 12.7 for 0% CO₂ and AZ, and 14.3 for 10% CO₂ and AZ (paired samples *t*-test; $p > .05$ for 0% CO₂ versus 10% CO₂; $p = .01$ for AZ versus without AZ).

	<i>Lowest O₂</i>		<i>PaO₂ (mm Hg)</i>	
	<i>Saturation (%)</i>			
	<i>0% CO₂</i>	<i>10% CO₂</i>	<i>0% CO₂</i>	<i>10% CO₂</i>
Without				
AZ	68.4 ± 19.6	71.7 ± 19.5	58.3 ± 7.9	59.6 ± 10.3
With AZ	78.0 ± 20.5	79.8 ± 19.1	69.0 ± 10.4	73.4 ± 11.6
p (AZ vs no AZ)	.003	.014	<.001	<.001
p > .05 for 10% CO ₂ versus 0% CO ₂ with and without AZ for all variables (paired samples <i>t</i> -test).				

There was no effect of level of oxygenation or of



Hypoxia shortened the mean apnea duration (paired samples *t*-test, $p = .025$); neither 10% intralaryngeal CO₂ nor AZ had an effect on the mean apnea duration when laryngeal stimulation was performed under hypoxic conditions (paired samples *t*-test, $p > .05$ for both; Fig 4). In addition, laryngeal

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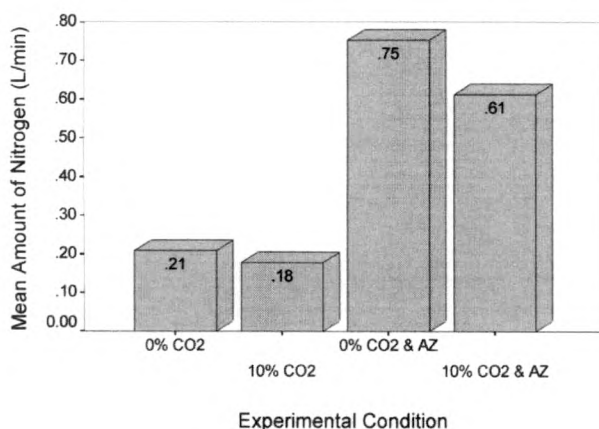


Fig 3. Effect of 10% intralaryngeal CO₂ and intravenous AZ on amount of nitrogen needed to create hypoxia (PaO₂ of 50 to 65 mm Hg; n = 11). Standard deviations were 0.081 for 0% CO₂, 0.068 for 10% CO₂, 0.36 for 0% CO₂ and AZ, and 0.20 for 10% CO₂ and AZ (paired samples *t*-test; *p* > .05 for 10% CO₂ versus 0% CO₂; *p* = .001 for AZ versus without AZ).

stimulation during hypoxia (0% CO₂) resulted in a lower PaO₂ level and a lower O₂ saturation level at the end of the apnea when compared with normoxic stimulation (paired samples *t*-test, *p* = .018 and *p* = .003, respectively; Table 4). Neither 10% intralaryngeal CO₂ nor AZ had an effect on O₂ saturation level or on PaO₂ level during the first recovery breath of hypoxic stimulation (paired samples *t*-test, *p* > .05 for each; Table 4).

There was no effect of hypoxia or 10% intralaryngeal CO₂ during hypoxic stimulation on ability to recover (Wilcoxon signed ranks test, *p* > .05 for both;

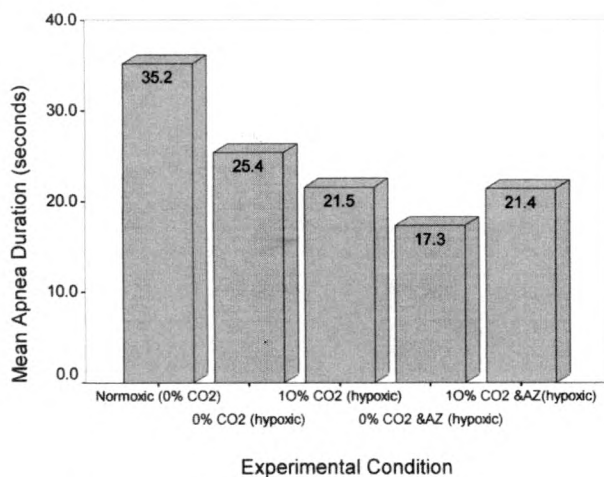


Fig 4. Effects of hypoxia (PaO₂ of 50 to 65 mm Hg) and of 10% intralaryngeal CO₂ and AZ during hypoxic stimulation on mean apnea duration (n = 11). Standard deviations were 25.2 for normoxic 0% CO₂, 23.5 for 0% CO₂, 25.4 for 10% CO₂, 13.5 for 0% CO₂ and AZ, and 25.8 for 10% CO₂ and AZ (paired samples *t*-test; *p* = .025 for hypoxia versus normoxia; *p* > .05 for 10% CO₂ versus 0% CO₂; *p* > .05 for AZ versus without AZ).

TABLE 4. PART 2: MEAN MEASURES DURING FIRST RECOVERY BREATH (N = 11)

	Lowest O ₂ Saturation (%)		PaO ₂ (mm Hg)	
	0% CO ₂	10% CO ₂	0% CO ₂	10% CO ₂
Normoxic trial	56.0 ± 22.5		52.3 ± 12.9	
Hypoxic trials				
Without AZ	47.3 ± 18.9	48.4 ± 19.9	40.6 ± 7.0	45.1 ± 5.9
With AZ	46.4 ± 27.3	47.2 ± 22.5	41.2 ± 6.8	39.8 ± 6.7
<i>p</i> (AZ vs no AZ)	>.05	>.05	>.05	.051

There was significant effect of hypoxia (0% CO₂ without AZ) versus normoxia (0% CO₂) on PaO₂ (*p* = .018) and on lowest O₂ saturation (*p* = .003). There was no effect of 10% CO₂ on any of variables in hypoxic trials with or without AZ (*p* > .05; paired samples *t*-test).

Fig 5). Injection of intravenous AZ, however, enhanced the ability to recover from the apneic response when stimulation was performed under hypoxic conditions, with the animals recovering from the apneic response without assistance 63.6% of the time with AZ, compared with 31.8% of the time without it (Wilcoxon signed ranks test, *p* = .038; Fig 5).

DISCUSSION

The introduction of 3% to 10% CO₂ into the surgically isolated upper airway of adult cats and dogs while the systemic PaCO₂ level is held constant results in decreased ventilatory activity.²¹⁻²⁹ The results of this study, however, show that 10% intralaryngeal CO₂ did not have any effect on ventilatory activity in 13- to 18-day-old piglets under normoxic

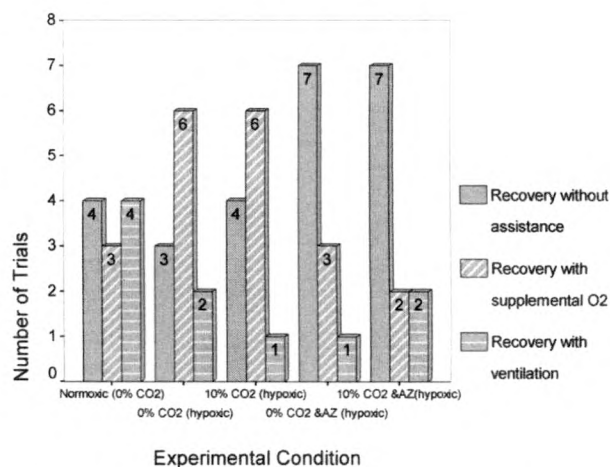


Fig 5. Effects of hypoxia (PaO₂ of 50 to 65 mm Hg) and of 10% intralaryngeal CO₂ and AZ during hypoxic stimulation on ability to recover from apneic response (n = 11; Wilcoxon signed ranks test; *p* > .05 for hypoxia versus normoxia; *p* > .05 for 10% CO₂ versus 0% CO₂; *p* = .038 for AZ versus without AZ).

or hypoxic conditions. This implies a lack of CO₂-sensitive laryngeal receptors in these young piglets. This difference in the effect of intralaryngeal CO₂ on ventilatory activity may be due to a maturational or a species difference between the animals in this study and those of prior studies. The observed absence of an effect of intralaryngeal CO₂ on the LCR is consistent with its lack of effect on baseline respiratory physiology.

In the piglet model, injection of intravenous AZ results in an increase in baseline PaO₂ level under normoxic conditions. During both normoxic and hypoxic conditions, AZ administration results in an increase in baseline respiratory rate, a decrease in baseline PaCO₂ level, and a stable pH. It is known that the inhibition of carbonic anhydrase by AZ interferes with the transport of HCO₃⁻ across the blood-brain barrier, resulting in a greater concentration of CO₂ and H⁺ ions at the medullary respiratory centers of the brain stem, thus stimulating the respiratory drive.^{32,36} The result is an increase in minute ventilation, vital capacity, and PaO₂ level.^{30-32,37} After receiving AZ, the piglets in this study required 3 times as much N₂ to create the same degree of hypoxia as they did before AZ injection. This is consistent with the increase in respiratory drive associated with systemic concentrations of AZ observed by others.^{30-35,37}

Under normoxic conditions, AZ also has a protective effect on the LCR. It shortens the mean apnea duration and prevents the systemic PaO₂ and O₂ saturation levels from falling as low during the apneic response as they do without AZ. The animals' ability to recover from the reflex-induced apnea without assistance is also enhanced with AZ under normoxic conditions. When the arterial PO₂ level is forced down to create hypoxia, the positive effects of AZ on mean apnea duration, recovery PaO₂, and O₂ saturation are negated. Despite this lack of change in apnea duration with hypoxic stimulation, the positive effect of AZ on the respiratory drive persists: it continues to enhance the animals' ability to recover from the reflex with spontaneous respirations and without the assistance of supplemental O₂ or positive pressure ventilation.

The level of oxygenation existing immediately before laryngeal stimulation has been previously shown

to affect the apneic response.¹⁸ Hypoxia will initially have a stimulatory effect on respiration, but if the central PaO₂ level declines too much, a depressant effect results. Overall, most animals tend to have a milder response to hypoxic stimulation, resulting in a shorter average apnea duration. However, profound or fatal apneas are more common under hypoxic conditions.¹⁸

The results of the present study show that laryngeal stimulation during hypoxia (PaO₂ of 50 to 65 mm Hg) results in a decrease in mean apnea duration and that a higher level of oxygenation before laryngeal stimulation results in a higher PaO₂ level at the end of the apneic response. Despite this effect on apnea duration and recovery PaO₂ level, hypoxia as defined in this study (mean prestimulation PaO₂ level of 58.5 versus 82.5 mm Hg) did not affect the ability to recover from the apneic response without assistance. These results suggest that the effect of AZ on the level of oxygenation during the LCR is related to its ability to stimulate the respiratory drive and create a greater degree of oxygenation at baseline. The ability of AZ to shorten the mean apnea duration and to enhance recovery from the reflex may be related to its inhibition of uptake of CO₂ in the brain. This would result in a greater concentration of CO₂ at the medullary respiratory centers during the apneic response, thus stimulating respiratory activity and shortening the duration of the LCR-induced apnea.

CONCLUSIONS

Ten percent intralaryngeal CO₂ has no effect on ventilatory activity or on the LCR in young piglets. Acetazolamide, however, has a protective effect on the LCR. When given to piglets, it decreases the mean apnea duration and increases the ability of the animals to recover from the reflex without assistance, likely by stimulating the respiratory drive. This effect of AZ on the respiratory drive results in higher baseline systemic PaO₂ and O₂ saturation levels. A higher level of PaO₂ at baseline protects the animal from a low PaO₂ level during the apneic response. Thus, this study suggests that perhaps methods of increasing the baseline level of oxygenation either with O₂ or with AZ may help in the prevention of profound and fatal apneas in infants who are at increased risk.

ACKNOWLEDGMENTS—We extend a special thanks to Kerri Johnson Pernell and Charles MacArthur for all of their efforts in helping to make this project possible.

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FUNCTION OF A HEARING AID UNDER STRESSFUL CONDITIONS

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The auditory function of individuals with normal hearing was compared with that of hearing-aided subjects of similar age to determine whether amplification remediates hearing impairment under stressful auditory situations. The specific tests of listening in a competitive noise environment and identifying moderately compressed speech were introduced to adequately aided individuals. The data indicate that noise had an impact on auditory function to a much greater degree in aided individuals than in matched counterparts with normal hearing. The data derived from acceleration of simple sentences delivered to the aided group suggested that contrary to basic tonal sensitivity, the capacity to understand the stimulus was greatly compromised. The authors discuss cochlear damage and central auditory impairment as they relate to the limitations of amplification for sensorineural hearing loss.

KEY WORDS — competitive noise environment, compressed speech, hearing aid.

Our study examined this issue: How does the hearing-impaired ear respond to amplification under adverse conditions? Specifically, we assessed 2 areas that were of virtually universal concern to hearing-aided individuals: 1) speech discrimination, that is, clarity of understanding during simultaneous exposure to a competitive noise environment, and 2) the capacity to hear and identify sentences composed of simple and common words when presented at a modestly accelerated rate.

Initially, we emphasize that this investigation does not include how to fit a hearing aid or the formulas for amplification and individualized frequency modulation. Neither do we examine or compare the varieties of hearing aids. Finally, we do not intend to recommend or suggest specific commercial products on the basis of this investigation.

We consider the results of this study applicable to the complaints of the hearing-aided subject. Most important, to clinicians who may be involved in the care of individuals with hearing problems, we suggest the limits of amplification, the margins of gain contingent on the nature and degree of the auditory disability, and, last, the boundaries of assistance and the need for suppression of exaggerated or unrealistic expectations.

It is obviously impossible to predict in advance the exact gain achieved by the subject through amplification because of the unique and individual forms of disorders within the auditory system. This nonhomogeneity of damage includes cochlear hair cell integrity, that is, damage of the outer and inner hair cells, and the status of the primary neuronal structures, such as cellular population and function. More

centrally, we recognize the components of auditory transmission through the brain stem and the thalamocortical radiations. Finally, a measure of the delayed far-field auditory-induced electrical activity may reflect the terminal cortical regions of sound recognition and speed of responsiveness or slowness of cognitive performance.

These functional issues vary among individuals, and the reported data from this investigation confirm our experience that comparable or similar audiometric patterns do not predict identical results under the sophisticated stress of the test complexities.

The diagnostic analysis of hearing deficits in the peripheral or central auditory areas or a combination thereof depends on specific dedicated tests that reveal the integrity and function of each component. We used the model for the framework of word identification by Pisoni and Luce.¹ This concept proposes that the sequence of events and analytic stages is initiated with peripheral auditory processing and proceeds to acoustic-phonetic and phonological analysis, thereafter to word recognition, and finally to lexical access. Normal performance is contingent on adequate quality and quantity of the received message. Defective performance at any stage before final integration into the word reservoir may cause a perceptual dysfunction.

The following data are based on the progression of hearing loss with age. The justification for this approach is the large database developed by longitudinal analysis over many years that defines the various functional disturbances in sensitivity, frequency analysis, speech and sentence discrimination, and hearing in competitive noise.

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We recognize that the etiologic factors of hearing impairment in young individuals are different from those in older patients with presbycusis. Nonetheless, the hearing impairment still reflects dysfunction of the same functional communication skills as in elderly subjects. In addition, 90% of the subjects in this report fall within the 7th to 10th decades of life.

Auditory function diminishes with age; this fact has been accepted for decades. The prevalence of age-related deafness is high, and the magnitude of the social and medical disorder increases with the progression of an aging population. Current data indicate that the incidence of hearing loss doubles per decade, beginning with 16% at 60 years of age and proceeding to 32% at 70 years of age and 64% at 80 years of age; few are spared hearing loss above 86 years of age.²

The evidence concerning hearing loss and age is briefly reviewed from a historical standpoint and in more current references to amplification.

Pure tone audiometry identifies a decrease in sensitivity beginning at about 30 years of age, primarily involving the frequencies above 1 kHz and with continual progression beyond 60 years of age. The earliest reports, by Bunch,^{3,4} described a peripheral deficit with the characteristics of symmetric hearing loss with wide variation in auditory sensitivity (ie, degree of loss) and little correlation with age. A more recent update on this topic was compiled by the Working Group on Speech Understanding and Aging.⁵

Speech discrimination is depressed with aging. A broad correlation between tonal sensitivity and word identification exists; however, exceptions and disproportions may be seen.⁶⁻¹¹ An analysis of speech perception in elderly patients through auditory and cognitive components discloses that in comparison with younger patients (18 to 28 years of age), the senior group (61 to 85 years of age) functions with greater individual variation, although considerable overlap is shown on tests of phonemes, spondees, and sentence perception. Also, the hearing loss of the elder group is largely related to high-frequency impairment.

Sentence identification is more impaired than single-word testing. This dysfunction may begin between 30 and 39 years of age and thereafter increases rapidly with each subsequent decade.^{11,12} The ability to identify sentences correlates with the linguistic structure of the stimulus, the meaningfulness of the phrase, the presence of overlying syntactic constraints, and, especially, the rate of presentation.¹² Consequently, as the complexity of the stimulus increases, accurate recognition falls. Conversely, simplicity of stimu-

lus, content, and structure corresponds with increased levels of identification.

The recognition of speech with simultaneous sentence competition begins to diminish in the fourth decade; the failing ratio increases slowly to the seventh decade and continues more rapidly thereafter.^{13,14} The individual influence of distortion caused by high noise competition is so variable that subjects with similar performance in quiet may differ substantially in noise. The impact of speech babble noise on sentence identification is similar to that of a competitive sentence, namely, a function of age and hearing loss.¹⁵ Deterioration of the suppression mechanism is considered to be the foundation for this depressed function.¹⁶ The influence of age on masking level difference is discussed as a factor in decreased sensitivity¹⁷ and relates to impaired binaural auditory processing, intensity of peripheral stimulus, and reduction in the awareness of interaural difference and binaural cues.¹⁶ Temporal distortion of the speech stimulus results from time compression, interruption of speech, and reverberation of the verbal signal. These modifications of presentation produce a relatively severe performance deficit in verbal identification that is correlated with aging. Recall of sentences by older adults was found to be disproportionately depressed by increased speech rates.^{11,12,18-20} The diminishing performance is explained by a processing rate deficit and a superimposed defect in organization and integration of the verbal input. The "time sampling" phenomenon, a notion that implies an adequate temporal exposure within the central auditory system, is a fairly simplistic concept that may be correlated with other cognitive defects of hearing noted previously. Amplification of the stimulus level to correct intelligibility of temporally distorted speech fails to improve verbal sensitivity.

More complex tests of binaural interaction and modification by frequency attenuation identify a progressive deterioration of function from the 7th to 10th decades. Presbycusis compounds the degree of performance deficit of the elderly during these examinations and may be correlated with the loss in tonal sensitivity. Our research suggests that increased loudness of the stimulus has limited value toward improvement of the dichotic input and identification of a distorted word stimulus.²¹

The effects of central auditory disability appear at a mean age of 60 years, with wide variation and progression thereafter. The consequences are observed in the more sophisticated aspects of hearing such as temporal modification of speech, simultaneous noise exposure, and rate of processing. Inadequate use of

temporal cues and speech perception,²² age-related behavioral slowness,²³ and the diminished capacity to retain or recall information are cited as contributing factors toward inadequate verbal discrimination.^{10,24,25}

Electrophysiological testing of auditory potentials in elderly subjects reveals a delayed wave V latency in patients 61 to 75 years of age that increases approximately 1.30 ms/y thereafter.²⁶ An additional morphological change corresponding to a decreased amplitude of 0.18 mV/y was identified.²⁷ Because diminished auditory processing may relate to the delay of the P-300 wave and simultaneous decreased voltage, we suggest that this observation may represent a defect in the cortical associations of hearing related to cognition.

When this study began and sufficient data were accrued for analysis, we concluded that with the then-existing instruments, and in the intervening years with new technology, amplification failed to solve hearing deficit in noise. Subsequently, Killion commented, "Hearing aids can solve the problem of loss of sensitivity..., but hearing aid circuits can not solve the SNR (signal noise ratio) problem caused by loss of inner hair cells or actual nerve deafness."^{28(p29)} Bentler assessed the hearing aid and stated that "in high levels of background noise no previous or current hearing aid processing strategy is capable of improving SNR, ie, separating the intended speech signal from the unaided noise signal."^{29(p10)}

MATERIALS AND METHODS

Each individual volunteered for the study, was not compensated, and had undergone a complete medical and otologic evaluation before entry into this project. The subsequent routine auditory studies included pure tone thresholds and speech discrimination. Thereafter, a hearing aid consistent with the demands of the patient was prescribed, and after several weeks for adaptation, evaluation of reception during noise and accelerated speech was completed. The audiological criteria for entry into the aided segment of this investigation included free-field speech reception thresholds at 25 dB sound pressure level (SPL) or better and a discrimination value greater than 70%. The performance requirements of the subjects with normal hearing used as reference to the aided individuals are contained in the subsequent section of data. These subjects are divided into 2 segments by the high-frequency function, although the speech reception threshold (SRT) and discrimination scores are quite similar.

The hearing-impaired subjects were classified according to the following criteria for speech recep-

tion, which were coordinated with pure tone averages: 1) mild hearing loss, that is, 25 to 35 dB hearing level (HL); 2) moderate loss, that is, 35 to 55 dB HL; and 3) severe disability, greater than 60 dB HL.

The focus of this report is on the second group, with a moderate loss, because in our experience this segment comprises the majority of hearing aid users, and the unaided function of auditory clarity is not markedly depressed (ie, greater than 75%). In addition to these factors, amplification usually improves the threshold of hearing to levels greater than 25 dB HL with some commensurate improvement in discrimination. Finally, the objective measurements of amplification under the adverse conditions of a testing situation are more consistent than in group 3 (severe loss), which has a greater disability in verbal sensitivity and accurate recognition. Although we do not present any data from the most impaired segment, these subjects failed to meet the criteria for entry, and when considered realistically, the functional disability is beyond complete remediation.

Additional stipulations for entry into the investigation included 1) unilateral amplification; subjects with hearing aids on both ears were eliminated to provide an accurate and unbiased assessment of the isolated 1-sided function; 2) the unaided ear must reveal an impairment greater than a 25-dB differential with the aided ear to eliminate crossover or binaural input; and 3) the test environment is constant, the measurement of speech is in a free field provided by paired speakers 45° azimuth from the midline, and there is negligible internal noise.

INSTRUMENTATION

Testing was performed in a custom sound-treated acoustic environment. The stimuli included live voice for the measurement of SRT, and Audiotec (St Louis, Mo) cassette recordings of NU-6 lists 1 through 4 for speech discrimination in quiet. Sentence compression was presented by an Audiotec recording of the 30% rate and the speech babble (background noise) from the same source. The tapes were played on a Realistic SCT-86 cassette tape recorder-player coupled to Grason-Stadler (Milford, NH) clinical audiometer GSI-61. Sound field presentation of the verbal stimuli was through a Bose (Blythewood, SC) RM II speaker system and TDH 39P earphones (Telephonic, Farmingdale, NY). All equipment was calibrated in accordance with ANSI 1989 standards.

PARAMETERS OF SPEECH STIMULUS

The intensity of speech presentation for the normal cohorts was 50 dB SPL, and for the aided subjects, sufficient amplification was added to the corrected SRT to effectively produce a 60-dB exposure level.

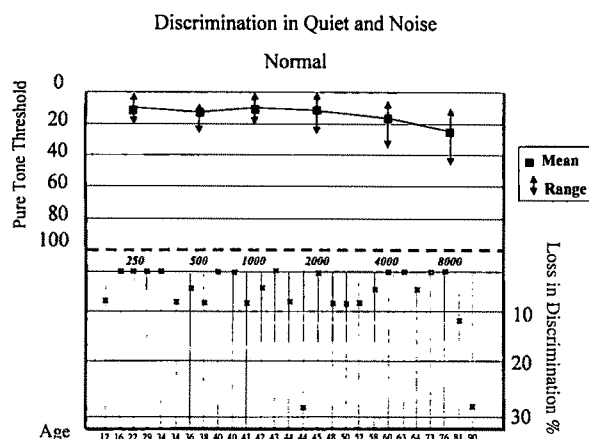


Fig 1. Composite audiogram of normal subjects illustrates mean levels and ranges of sensitivity. Individual ages extend from 12 to 90 years. Lower graph confirms little negative impact on hearing in noise (+10-dB signal-to-noise ratio).

SOUND-NOISE RELATIONSHIP

We selected a 10-dB signal-to-noise ratio (SNR) for this investigation. In general, the speech stimulus was presented at approximately 40 dB over the aided threshold response; the corrected range was thus between 55 and 65 dB HL.

The SNR of 10 dB that we have used for the past 5 years appears to be adequate for verbal speech understanding. Killion²⁸ considered the SNR required for 50% word recognition as a function of hearing loss. The linear curve for the incrementally required stimulus gain versus noise begins at a 20-dB loss. At this point, the value is approximately 5 dB, which increases to less than 10 dB at a 60-dB loss. At this level, an accelerated SNR is required for recognition beyond the approximately 70-dB threshold sensitivity. The quality and composition of the competing noise stimulus is relevant to this study. In the past, we have used broad-spectrum noise and a low-frequency background; currently, we use the simultaneous recording of 3 male voices and 1 female voice in a babble presentation (Auditec), which we have determined to be realistic and paralleling the tested words in frequency composition.

The compressed speech test was used by Beasley et al^{30,31} in the evaluation of central auditory perceptual disorders. In addition to this application, Sticht and Gray³² examined time compression with respect to age and hearing loss. They concluded that attenuation of performance in elderly subjects was greater than that in young subjects, whereas the nature of the subjects' hearing loss did not affect the capacity for comprehension. The tape presents both 30% and 60% compression segments. We determined that the higher compression level was incomprehensible to almost all of the aided subjects and to many of the

normal-hearing subjects, particularly elderly subjects; consequently, we deleted this rapid rate of presentation. The reported results are derived from the 30% compression sentences, which are presented in 10 sentences and are scored at 10% per unit. The individuals with normal hearing are actually measured by binaural input, and to a modest degree, the results are measurably better (less than 20%) than those for the subjects with a comparable monaural stimulus. A later report will consider the impact of competitive noise, environment, and understandability on profound unilateral deafness, but this presentation is primarily designed to evaluate individuals with 1 hearing aid and the negative influence of a "stressful" exposure to ambient noise.

RESULTS

We divided the data into 3 categories. Group A included individuals with normal hearing within 25 dB SPL in the frequency range of 250 to 4,000 Hz, maximal losses of 25 and 35 dB, respectively, at 4 and 8 kHz, an SRT of >20 dB, and discrimination of $\geq 90\%$. Group B included individuals with a loss of >45 dB at 4 and 8 kHz, an SRT between 20 and 30 dB, and discrimination of $\geq 88\%$. Group C was the hearing-impaired cohort with unaided sensitivity (SRT) of between 30 and 55 dB HL and a discrimination score of >70%.

Early in the 5-year study, we observed the obvious impact of competitive noise on subjects with normal hearing. The common denominator in subjects who had depressed function in noise was identified as a high-frequency loss of sensitivity. Consequently, this group was separated from the totally normal subset (defined above), and comparisons of performance were made between the 2 categories (A and B) and the aided hearing-impaired subjects.

A similar observation was drawn from the investigation of auditory performance under the challenge of compressed speech. The data from the 3 groups were compiled and examined by individual and group performance.

INFLUENCE OF NOISE

Normal Hearing and Noise (Group A). This group included 27 individuals from 12 to 90 years of age (mean, 47.25 years). The basic composite audiogram reveals the mean pure tone sensitivity per frequency and the range of function of the group. The lower compartment of Fig 1 identifies the impact of noise on clarity. These figures are presented by age and score. Thirteen of the group had minor and probably insignificant depression of scores (less than 10%). Two subjects, 44 and 90 years of age, had some loss (28% each) as a result of the competitive noise.

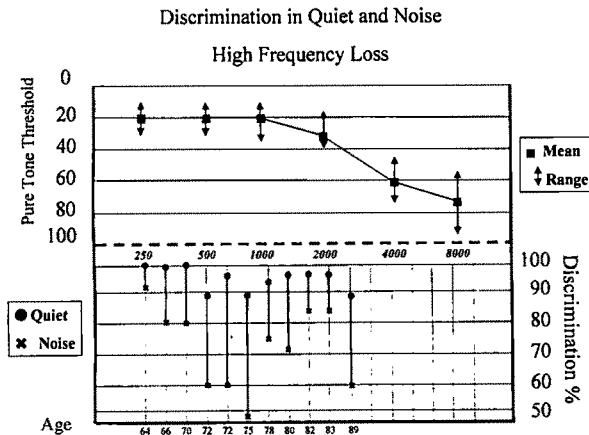


Fig 2. High-frequency loss of sensitivity is noted in audiometric pattern at 4 and 8 kHz. Impact of noise on these subjects reveals variable and individual loss of function extending from less than 10% to 50%.

Impact of Noise on High-Frequency Loss (Group B). This group comprised 11 subjects from 64 to 87 years of age (mean, 75.5 years). Figure 2 shows the configuration of the pure tone sensitivity, the mean range, and the gradual depression of the higher-frequency responses. A loss of auditory reception due to the influence of noise is confirmed by the graph, which suggests a negative impact on each individual of variable degree. The mean loss consequent to competitive noise exposure is 21%, with a range of 4% to 40%.

Aided Discrimination in Quiet Versus Noise (Group C). Nineteen individuals were evaluated in this group. Their ages ranged from 24 to 96 years (mean, 72 years). Sensorineural hearing loss was the major deficit that required amplification, although two individuals had conductive losses as a result of congenital aural malformations or advanced destructive middle ear disease. The cochlear functions were generally within group B criteria, that is, high-frequency loss.

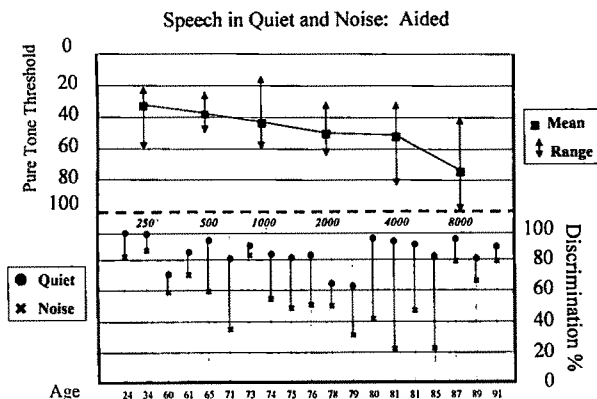


Fig 3. Composite mean audiogram of hearing-aided group confirms impaired sensitivity beyond normal range in each frequency. Lower graph depicts age and function and confirms loss of sensitivity with wide individual impact and variability due to simultaneous competing noise.

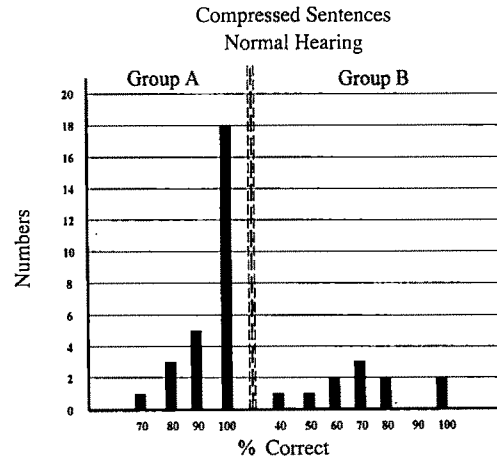


Fig 4. Negative impact on understanding of compressed sentences is negligible in subjects with normal hearing (group A). High-frequency loss group (group B) is significantly impaired in this simple auditory challenge.

Since this segment (2 patients) with the mixed form of deafness, ie, sensorineural and conductive loss, was not statistically significant, comparisons were not drawn. Nonetheless, the responses were consistent with the larger segment of the sensorineural hearing loss subset.

A wide range of disability is evident in Fig 3; the depression of function extends from very severe (>40%) to a relatively minor loss of 20% in noise. Nonetheless, 53% of the aided individuals were moderately to severely compromised, with >30% loss of sensitivity caused by the competitive effect of noise.

IMPACT OF COMPRESSED SPEECH

Subjects With Normal Hearing and High-Frequency Loss. The individuals in groups A and B are integrated for comparison in this section, and the performance of the normal responders is compared with that of subjects with high-frequency loss (Fig 4). Although the numbers are not equal in groups A and B, an obvious difference in function is clearly noted. The preponderance of group A (85%) responded accurately to the sentence task, with a score of 90% or

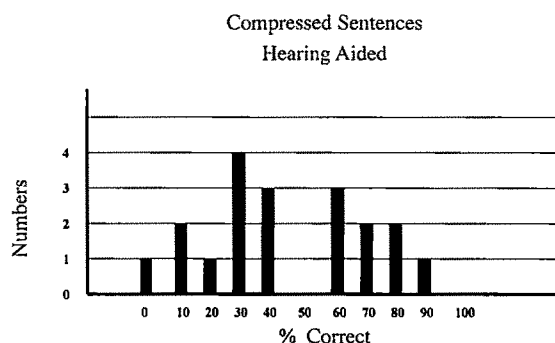


Fig 5. Hearing-aided subjects present wide range of functional loss; majority of group understands less than 50% of test.

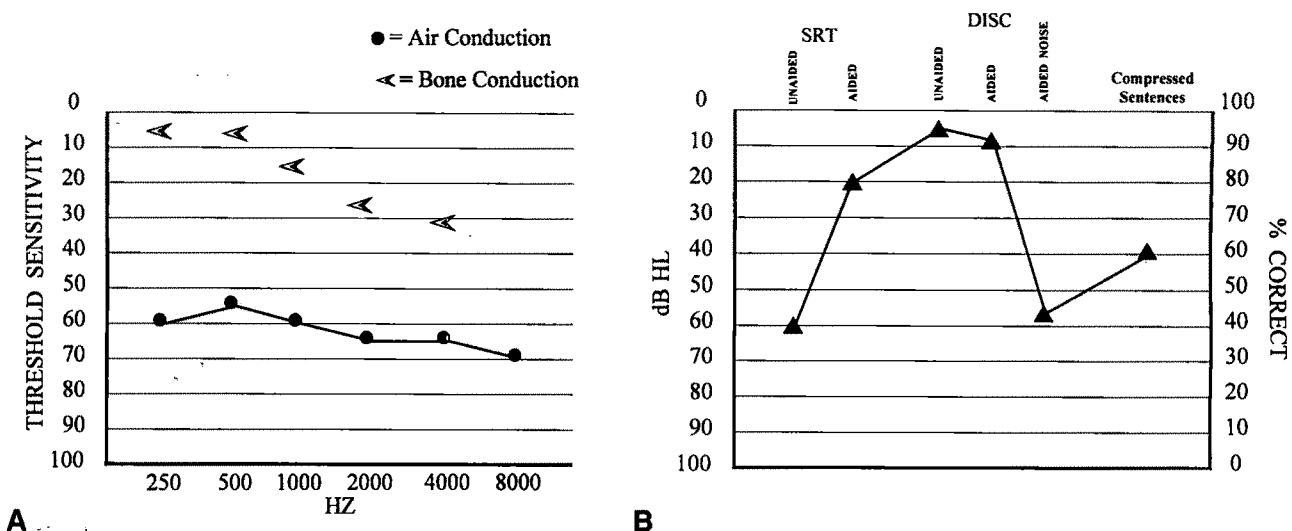


Fig 6. (Patient 1) 24-year-old man with Treacher Collins syndrome and external canal atresias. SRT — speech reception threshold. A) Audiogram reveals 50-dB air-bone gap and mild loss of sensory function in higher frequencies. B) Comprehensive auditory analysis reveals excellent sensitivity in discrimination (DISC) after amplification. Significant loss (44%) of verbal communication due to competing noise is noted, and compromised function is shown on exposure to accelerated sentences.

above. The high-frequency loss group, in contrast, had a mean score of 71%, with a range of 40% to 100%.

Hearing-Aided Subjects and Compressed Speech.

Figure 5 depicts the failure of communication from the presentation of moderately accelerated sentences. The mean score is 45%. However, the majority of this group, 11 of 19 subjects, function at or below the 40% accuracy value.

INDIVIDUAL CLINICAL RESULTS

We cite 5 cases of hearing impairment in the following clinical synopses and include age, calibrated measures of loss, etiologic factors when available,

and the results of amplification. We present these individual cases and their functional reports (Figs 6-10) to validate our thesis that the gains achieved by amplification are not homogeneous, despite parallel levels of sensitivity (by SRT) and intelligibility (discrimination). The data indicate wide differences in aided hearing in noise and in identification of compressed sentences, a much more realistic assessment of hearing aid function. A partial explanation for the disparity of results may be the different underlying pathophysiological disorders, as well as the specific frequency sensitivities.

Patient 1 was a 24-year-old man in whom Treacher

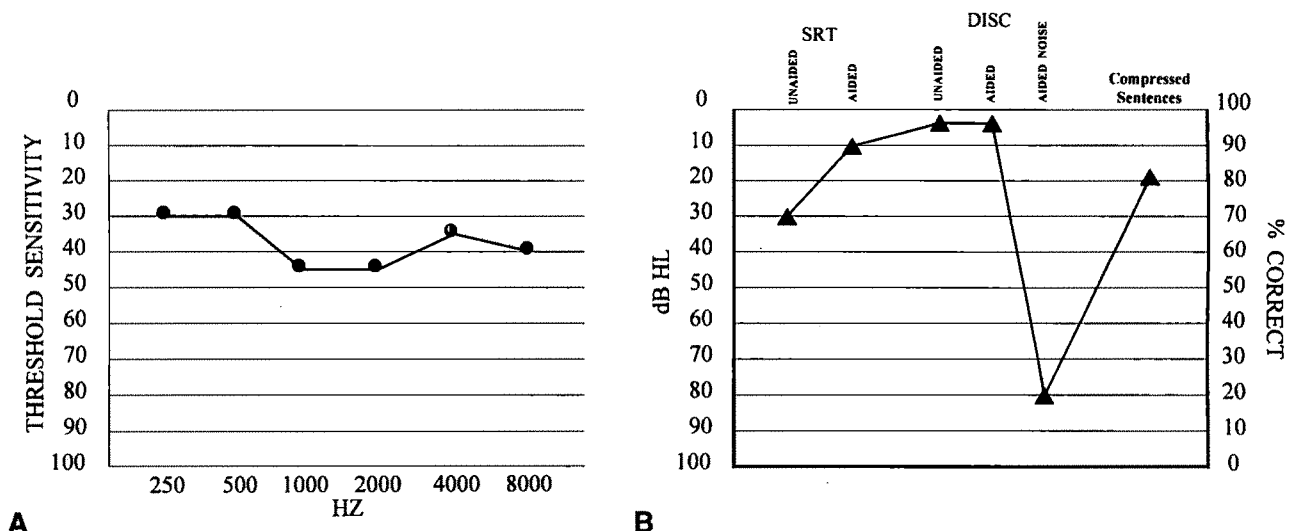


Fig 7. (Patient 2) 35-year-old man with bilateral sensorineural hearing loss of genetic origin that had slowly progressed during past 10 years. A) Curve identifies relatively flat threshold response. B) Aided response to 10 dB hearing level (HL) and excellent discrimination (96%) is severely degraded by competing ambient noise (20%), for net loss of greater than 70% intelligibility. Satisfactory function is shown on compressed sentence challenge (80%).

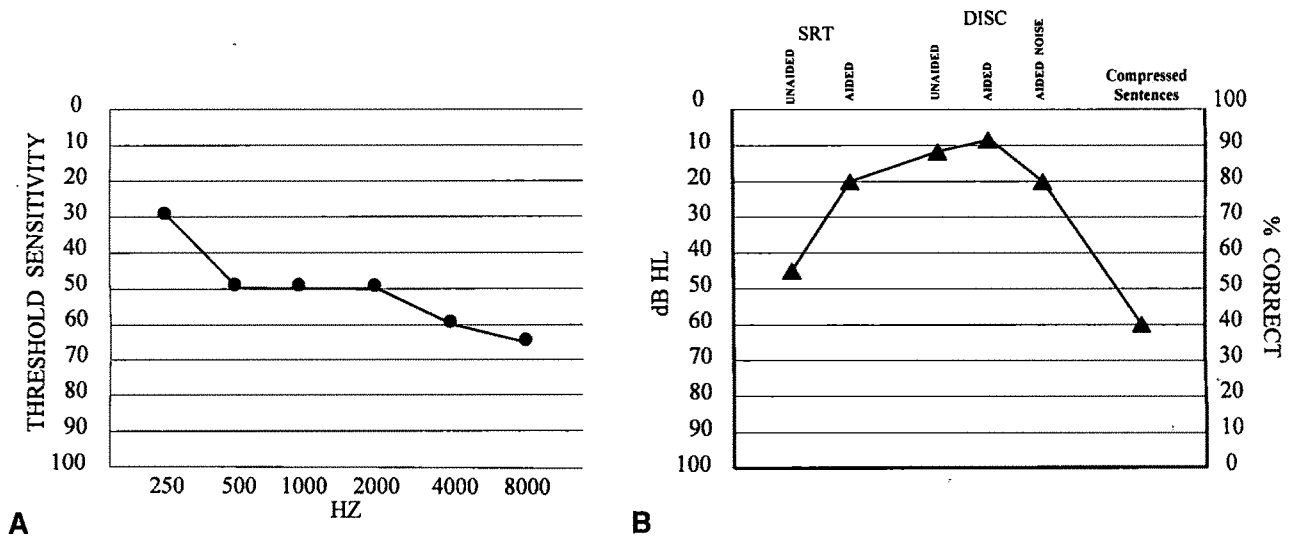


Fig 8. (Patient 3) 87-year-old woman with progressive hearing loss of more than 40 years. A) Current evaluation reveals mild falling curve at 4 and 8 kHz. B) Excellent gain in sensitivity and discrimination are noted with amplification. Minor depression in communication (10%) is measured in noise. Capacity to identify compressed sentences is seriously impaired.

Collins syndrome had been diagnosed. He was classified by our hearing criteria as low-level class B, with an SRT of 55 dB and excellent discrimination. The right ear revealed a narrow canal with a bony plate replacing the tympanic membrane. The left ear was totally atretic, with a small dimple in the lateral canal region. Because of this deformity, the patient wore a behind-the-ear aid on the right ear. The pure tone audiogram (Fig 6A) confirmed the completely obstructive component of the deformity with a resulting relatively flat air-conducted response and a mild sensorineural loss extending to 30 dB at 4 kHz. The performance data confirmed the aided response to a satisfactory functional level, adequate discrimination when aided, and a severe functional depression in

the aided noisy environment. A similar defect is reported in the compressed sentence test (Fig 6B).

Patient 2 was a 35-year-old man who had worn a hearing aid for 10 years as a result of progressive autosomal dominant genetic sensorineural deafness. The pure tone audiogram confirmed the degree of loss, and the speech discrimination score was excellent (96%; Fig 7A). The aided results clearly showed an improvement in hearing in a quiet situation or in low ambient noise; a dramatic loss in function was scored, to 20%, as competitive noise was introduced. In a quiet environment, the compressed sentence understandability was satisfactory (80%; Fig 7B).

Patient 3 was an 87-year-old woman who had had

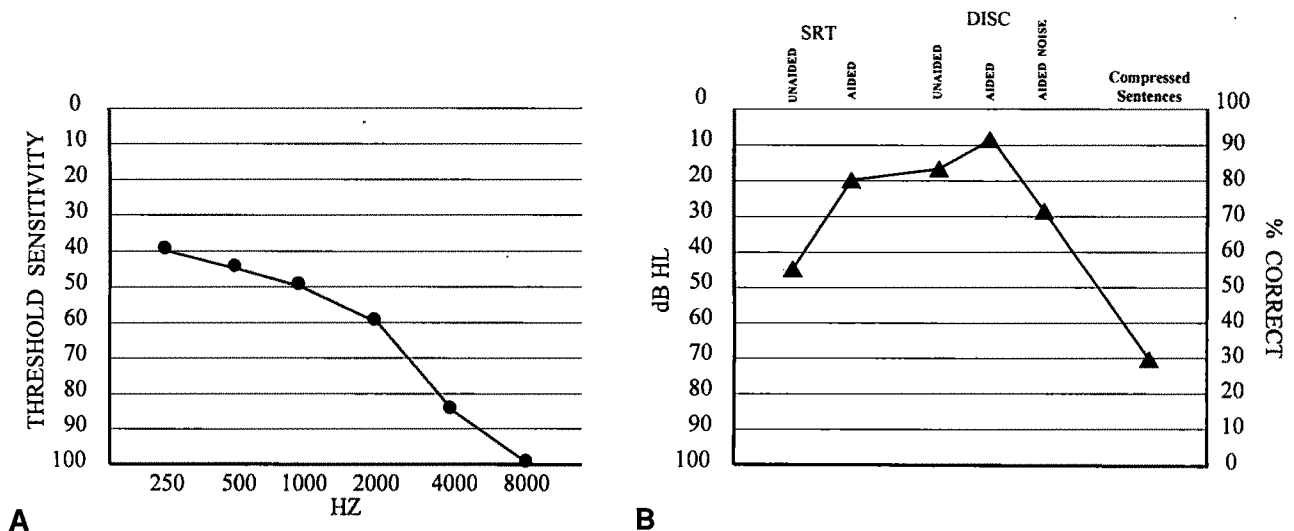


Fig 9. (Patient 4) 73-year-old woman with disabling sensorineural hearing loss and advanced presbycusis. A) Threshold response. B) Results of amplification are satisfactory. Sensitivity and discrimination are elevated to adequate functional level. Competing noise diminishes speech identification by 20%. Compression of sentences seriously interferes with intelligibility (30%).

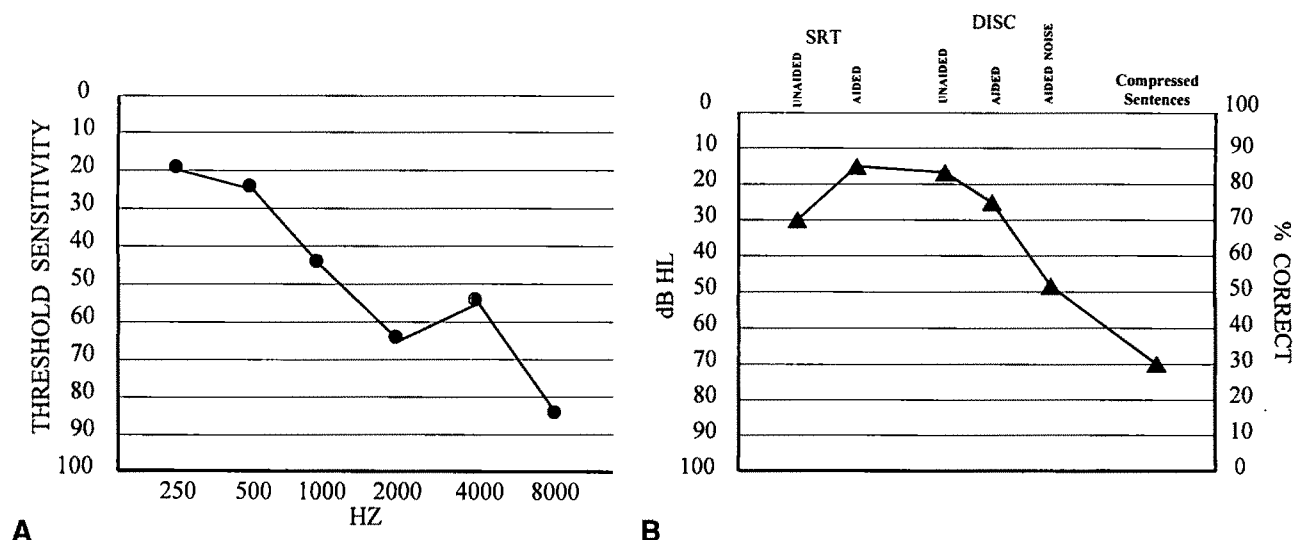


Fig 10. (Patient 5) 81-year-old man with sensorineural hearing loss. A) Audiometric data likely indicate presbycusis. B) Impact of noise on aided speech sensitivity is modest (10%), but recognition of compressed sentences is severely compromised (30%).

progressive hearing loss for more than 40 years and had been wearing a hearing aid for more than 20 years. In spite of the degree of sensorineural impairment, the discrimination score was 88% (Fig 8A). The composite scores confirmed a very satisfactory gain in function and minor impact on speech in the noisy environment; in contrast, the ability to accurately reproduce sentences was severely impaired (40%; Fig 8B).

Patient 4 was a 73-year-old woman who had worn a hearing aid for many years because of progressive sensorineural loss, which was most significant in the frequencies higher than 1,000 Hz (Fig 9A). The performance scale suggested adequate amplification, satisfactory discrimination in quiet, and a loss of clarity due to competitive noise (20%). The ability to identify single sentences was markedly compromised despite adequate amplification (30%; Fig 9B).

Patient 5 was an 81-year-old man whose hearing loss was characterized as having a steep, falling pattern with maximal loss in the high range (Fig 10A). The gain in different milieus confirmed adequate improvement in sensitivity. There was a minor loss of aided discrimination compared with the unaided state, and a significant loss in the noisy environment (approximately 35%; Fig 10B). The intelligibility of compressed sentences was seriously impaired in the aided mode, as confirmed by the 30% identification score.

A subjective questionnaire of satisfaction was presented to these 5 individuals; there was unanimous agreement that the hearing aids were successful in single-person contact or small groups but failed dramatically in areas of noise; poor acoustic environments, such as churches or meeting halls; and large

social events. Although this subjective assessment is anecdotal, we believe that the conclusions reflect the common observations of most hearing aid users. The individual data confirm the subjective complaints by objective measures in the environmental situations in which the aided subjects live.

DISCUSSION

This rather fundamental study investigated whether hearing aids help patients to function in a difficult environment compatible with life's daily sound exposure. We have simulated this experience with routine, as well as more sophisticated, techniques of advanced audiometry. Noise is ever present and with varying degrees of intensity, and we must function in this environment. The modes of verbal communication extend from the clear, articulate style to the distortion of mumblers and the rapid staccato of fast speakers. Aided subjects were tested with these verbal challenges with adequate amplification. A quantitative measure of performance was then assessed.

Initially, the normative data are presented, which indicate the difficulty hearing in noise and the impacts due to acceleration of sentences. The data verify the simplicity of both segments of auditory function by the consistently high score in group A and the evident impact of high-frequency loss in group B. The aided group, C, responds accurately in quiet and fails in a noise situation. The data are consistent, and additional studies not included within this report further corroborate these conclusions.

A separate auditory phenomenon, the ability to understand accelerated sentences (compressed), followed the same pattern as speech in noise, although

an apparent relationship between hearing in noise and recognizing accelerated speech was not identified in those with impaired high-frequency hearing or in the hearing-aided group. Group A, irrespective of age, reproduced the stimulus accurately, group B had a greater frequency of error, and group C had an even more apparent loss of sensitivity.

The individual performance data were illustrated to indicate the variability of response, the unpredictability of auditory improvement by amplification, and the negative impact of extraneous factors, such as environmental noise and the method of speech presentation, on the understanding of verbal communication.

It has been suggested that during the hearing aid assessment subjects should be measured in competing noise.²⁸ We recognize that the relative loss of discrimination induced by a +10-dB SNR may result in a mild to severe degree of impairment in communication. An additional sequel to this masking effect was the aided listener's subjective decision that the hearing aid was not functioning appropriately with the sequel of rejection of the otherwise satisfactory performance. The authors have additionally tested the subjects with normal hearing and hearing-aided individuals in +5 dB, 0 dB, and -5 dB SNRs. The impact of increased noise through this incremental gain was so dramatic that few words were identified. This observation further supported the contention that failure to hear in noise is a "real" phenomenon. As a consequence of these data and subjective observations, we have rejected the speech-in-noise test as a routine for the aided on the basis of the often discouraging results reported by individuals with impaired hearing.

How do we interpret these data with functional concepts, and what application does this information suggest for individuals with hearing aids? Initially, it is obvious that amplification can improve the sensitivity and clarity of speech discrimination. The results are contingent on the acoustic environment. This positive gain also depends on the underlying pathophysiological mechanisms that produce deafness. Although the performance at each locus, including the functional segments within the auditory cascade from the brain stem to the level of cognition, may not be precisely measurable, nonetheless, the dichotomy of peripheral versus central deafness may be entertained. Poor tonal responsiveness associated with seriously depressed speech discrimination usually points to a peripheral source of deafness. Central auditory dysfunctions may be investigated by more complex scenarios that include isolation of wanted data from an unwanted background (speech

in noise), integration of binaural separate information (dichotic presentation), distortion of speech by selective frequency filtration (frequency alteration), and rapid presentation of sentences.

Moderate peripheral function is essential for the transmission of data to the central auditory nuclear aggregate. Relative failure of the peripheral system results in poor central results; consequently, in this instance, the status of the central system remains unclear. The most dramatic audiological evidence in this cohort is seen in the competing sentence study, which generally reveals complete failure of binaural simultaneous audition. At this time, however, we do not suggest that the central studies of audition may reflect the capacity for aided hearing, but rather, that they are of relatively minor value, because amplification does not correct the central dysfunction.

Although the mechanisms of central suppression of cochlear activity as a result of environmental noise may not be completely understood, the olivocochlear efferent bundle may dampen the hair cell activity, thus improving recognition of speech. Saturation of the auditory system by competing unwanted noise under this hypothesis interferes with isolation of the wanted data, that is, speech. When we apply these concepts to individuals with sensorineural deafness, we begin with a dysfunctional cochlea with diminished sensitivity and impaired transmission via the auditory pathways to the auditory cortex. We suggest that the response from the efferent system for attenuation of noise is diminished in accordance with the primary disorder and the neural (cochlear) response consequent to stimulation. This thesis then attributes the failure of a pathological cochlea to hear in noise, which our data substantiate, to a peripheral loss of function and a central failure (efferent pathways) of cochlear suppression.

We believe that the auditory performance evaluated by compressed speech represents the capacity to function with a more efficient neural mechanism, that is, the speed of response with adequate isolation of data for identification and central recognition. We submit that this function is independent of the isolation of words in noise. The aided young subjects 27 and 35 years of age functioned with some degree of disability, 60% and 80%, respectively, whereas the patients older than 80 years of age responded at 40%, 30%, and 30%. These data may reflect an age impact, although few conclusions can be drawn from this small sample. In addition, the consequence of high-frequency loss (group B) is some degree of disability. The data in this group revealed a wide spectrum of results, from 40% to 100%. The analysis of the total cohort of 19 aided subjects, with a range of

0% to 90%, suggests a progressive failure of function with age. This conclusion was previously reported in an investigation on central deafness.²¹

It is noteworthy that the Food and Drug Administration (FDA), through the FDA Modernization Act of 1997, exempted manufacturers of hearing aids from premarket notification requirements.³³ The consequence is that marketing claims for new products may be promulgated without FDA clearance, although challenges to the advertisements must be answered by appropriate documentation.

The governmental decision clearly represents a caveat to the purchaser and suggests a discriminating assessment of hearing aid advertising. The members of multidisciplinary teams dedicated to the correction of hearing loss should critically analyze the purported assertions of success.

In summary, we have demonstrated that amplification by hearing aids often fails to maintain in noise the quality of reception achieved in quiet. In addition, when the stimulus is provided at 50 to 60 dB HL and is louder than the ambient noise by 10 dB, the impact, although of minor influence on subjects with normal hearing, is significant for those with hearing aids. Finally, as the intensity of the masking back-

ground increases, the intelligibility falls dramatically.

Equal intensities of noise and the speech stimulus tend to cancel the verbal reception. The means of remediation at this time are limited by the residual function of the peripheral auditory system and the distorted or incomplete neural response for central propagation of the auditory coding. Second, dysfunction of the central perceptual areas of hearing may negate or minimize the potential for amplification to an adequate level of intelligibility.

We suggest that the combination of peripheral and central hearing disorders further limits the potential gain by amplification. Perhaps transcochlear amplification with the numerous technological modifications, both current and anticipated, including directional and multiple microphone arrays, has approached the zenith of success. Finally, we confirmed that at this time, the improvement by amplification is contingent on the competence of the cochlea and the functional audiologic information (unaided) that define the potential for improvement. The additional examination of aided individuals in a noisy environment and with modestly compressed sentences defines the real value of amplification and the functional capacity in the various environmental modes of exposure.

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RUPTURE PRESSURES OF MEMBRANES IN THE EAR

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The rupture pressures of the tympanic membrane, Reissner's membrane, the round window membrane, and the annular ligament have all been measured in cadaver ears from Norwegian cattle. For the tympanic membrane, a static overpressure was applied to the ear canal; for Reissner's membrane, to the endolymph; and for the round window membrane, to the perilymph. The rupture pressure of the annular ligament equals the rupture force to the footplate divided by the area of the oval window. The mean rupture pressures are 0.39 atm for the tympanic membrane, 0.047 atm for Reissner's membrane, greater than 2 atm for the round window membrane, and 29.4 atm for the annular ligament. This last pressure corresponds to 0.68 kilogram force applied to the footplate. The ruptures of the tympanic membrane appeared without exception as small tears in the pars flaccida. The rupture pressure of the tympanic membrane was also measured in a few ears from foxes.

KEY WORDS — annular ligament, Reissner's membrane, round window membrane, rupture pressure, tympanic membrane.

INTRODUCTION

The rupture pressure of the tympanic membrane of animal and human ears has been measured by several experimenters using static and dynamic pressures.¹⁻⁶ Rupture pressure data of other membranes in the ear are sparse or missing.^{7,8} The aim of the present work is to add knowledge to this field and to present suitable measuring methods. Cadaver ears from NRF cattle, a Norwegian breed, were used in the experiments.

MATERIAL AND METHODS

Applying Cement to Ear Bone. To ensure attachment of the cement to the bone, the soft tissue is removed from the contact area, which is then carefully dried with paper towels. To improve the attachment, some Loctite 401 (Loctite Corporation, Dublin, Ireland) is applied. Plastic padding elastic (Loctite Sweden AB, Göteborg, Sweden) is used as a cement. It hardens in about 10 minutes, or even faster if a greater than normal amount of hardener is used. To avoid leakage from the perilymphatic duct and the inner ear meatus, the surrounding tissue and bone are carefully dried, and Loctite 401 is applied before the openings are coated with cement.

Rupture Pressure of Tympanic Membrane. The measurements are performed with an open middle ear. A glass tube is cemented to the ear canal. The glass tube is also connected to a 50-mL syringe and to a water-filled manometer (Fig 1). By opening 2 gate valves, atmospheric pressure P_0 is established

in the ear canal and the manometer tube. The valves are then closed and the pressure $P = P_0 + \Delta P$ in the ear canal is increased by manually pressing the syringe piston. For tympanic membranes with higher rupture pressures than those in cattle, the pressures attainable in this way may be too low. The maximum level difference h is read when the tympanic membrane ruptures. The location and shape of the rupture is observed through a microscope.

Let all pressures be expressed in meters of water. Assuming that the air in the manometer tube is saturated with water vapor with saturation pressure p , and using the isothermal ideal gas law for the partial

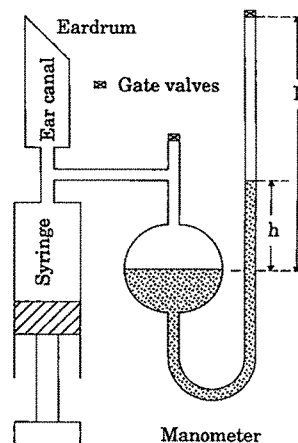


Fig 1. Measuring rupture pressure of tympanic membrane. With open gate valves, air-filled part of manometer tube has length L , corresponding to manometer level difference $h = 0$. After both gate valves have been closed, h is increased by pressing syringe piston.

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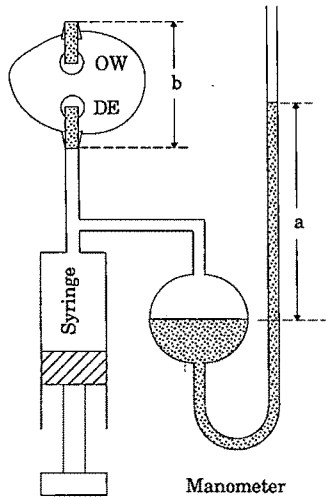


Fig 2. Measuring rupture pressure of Reissner's membrane. Initially, manometer level difference a is 0. After ear bone has been connected to manometer, a is increased by pressing syringe piston. For $a = b$, pressure difference across Reissner's membrane is 0. OW — oval window, DE — ductus endolymphaticus.

pressure of dry air, the rupture overpressure in the ear canal becomes

$$(1) \quad \Delta P = \frac{P_0 - p}{L/h - 1} + h$$

For the apparatus used, $L = 1.055$ m. At 20°C , p is 0.24 m water, and appears as a small correction to the atmospheric pressure P_0 of about 10 m water. An even better manometer liquid is oil, which has a much lower saturation pressure.

Rupture Pressure of Reissner's Membrane. The ear bone is cut parallel and close to the eardrum, so that a direct view to the oval window is obtained. The endolymphatic sac is cut close to the opening of the duct. A small steel tube is guided into the sac and cemented to the bone. It is important to avoid blocking of the tube by air bubbles or tissue pressed against its inner opening. Water from a syringe is therefore sprayed into the tube so that air bubbles are driven out and replaced by water. A male syringe cone terminates the steel tube opening, which is temporarily closed by a female syringe cone cover cap.

The footplate is removed from the oval window by penetrating it with a sharp-tipped tool and withdrawing it piece by piece. A steel tube is cemented to the oval window, and air is driven out from the scala vestibuli and the tube in the same way as explained above.

The cover cap is removed from the first tube and replaced by a female syringe cone connected by a silicone tube to a water-filled manometer and a 20-mL syringe (Fig 2). The syringe pressure is then increased while the water surface in the oval window

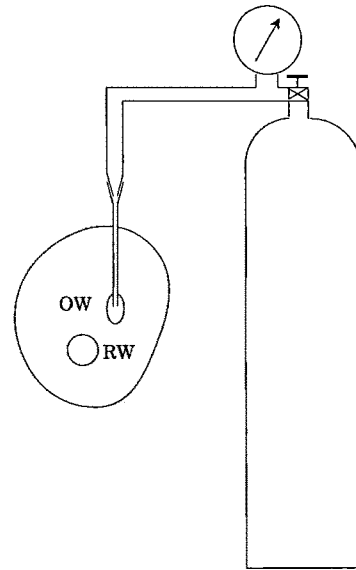


Fig 3. Measuring rupture pressure of round window (RW) membrane.

tube opening is observed through the microscope. The rupture pressure across Reissner's membrane is determined as the smallest pressure that gives a minute but continuous water stream out of the oval window tube:

$$(2) \quad \Delta P = a - b$$

Here a is the corresponding syringe overpressure and b is the height difference between the openings of the oval window and the endolymphatic duct tubes. As the pressure is increased in 5-cm steps, 2.5 cm is subtracted from the average result.

Rupture Pressure of Round Window Membrane. The ear bone is cut parallel and close to the eardrum, so that a direct view to the oval window is obtained. In order to prevent leaks, the openings of the perilymphatic duct and the internal auditory meatus are coated with cement. The stapes footplate and some perilymph are removed. A syringe needle (eg, 1.1×40 mm, rounded off at the tip) is cemented to the oval window and connected via a male syringe cone to a silicone tube and a gas cylinder with an output pressure gauge ranging from 0 to 2.5 bar (Fig 3).

The overpressure from the gas cylinder to the inner ear is increased until the round window membrane ruptures or until the maximum attainable pressure is reached. The highest attainable pressures will in most cases cause the inner ears to leak. Even higher pressures are therefore of minor interest. To exclude misinterpretation of other leaks, the rupture of the round window membrane should be confirmed under the microscope.

Rupture Force and Pressure at Stapes Footplate. The ear bone is cut parallel and close to the eardrum,

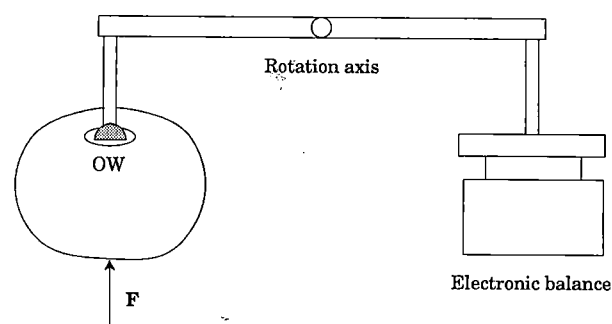


Fig 4. Measuring force (F) that causes annular ligament in oval window to rupture.

so that a direct view to the oval window is obtained. The stapes is removed, except the footplate, which is dried with "needles" of absorbent paper toweling. A small amount of cement is applied and hardened in order to distribute the pressure of the carefully applied force from a 1.1-mm-diameter syringe needle, which is cut flat at the pointed nose. The needle is attached to the end of a lever arm. At the end of another, equally long lever arm, a similar syringe needle rests with its cone end at the table of an electronic balance (Fig 4). When the handheld ear bone is pressed upward with a force F, both needles will act downward with the same force. The force is slowly increased until the annular ligament ruptures. The footplate will then be pushed into the inner ear. The rupture force, expressed in kilogram force (kgf), is read directly from the electronic balance, and the rupture pressure is obtained by multiplying by the constant of gravity and dividing by the window area.

RESULTS

Rupture pressures of membranes in ears from Norwegian cattle are shown in Table 1. Table 2 shows data related to rupture of the annular ligament. The mean tympanic membrane rupture pressure in a few ears from polar foxes (0.515, 0.561) and blue foxes (0.536, 0.639, 0.714) was 0.59 ± 0.08 atm.

DISCUSSION

In all experiments, the pressure has been slowly

increased. The rupture pressures have therefore been reached under almost static conditions. The mean rupture pressure of the tympanic membrane in Norwegian cattle, 0.39 atm, is appreciably lower than that in human ears, and also smaller than that in foxes, 0.59 atm, and that in some other smaller animals such as dogs, monkeys, sheep, and goats,^{3,5} but larger than that in cats.³ The rupture pressures of human tympanic membranes were thoroughly examined by Zalewski¹ in 1906. The results, which are in fair agreement with those from a later study by Jensen and Bonding,² are illustrated in an informative way in Fig 5. The number of ears, the mean rupture pressure, and the range are indicated in each 10-year age interval.

Above 20 years, the age dependency is small (-0.00115 atm per year) and less than that found by Jensen and Bonding² (-0.00487 per year). The regression line is based on the mean rupture pressures and the number of ears in each of the 10-year age intervals.

Below 20 years, the rupture pressure increases substantially with decreasing age. Above 20 years, the average rupture pressure is 1.4 atm. The mean for all ears is 1.59 atm. Zalewski¹ measured the rupture pressure within 24 hours of death.

The ruptures of the tympanic membrane in Norwegian cattle (and in fox ears) appeared without exception as small tears in the pars flaccida, as opposed to in human ears, in which 99% of the ruptures are localized to the pars tensa.² In the pars flaccida region, restoring forces will close the hole when the pressure difference is removed. This is supposed to further the healing process in living animals. In many cases, a hole in the pars flaccida will not be reopened but will remain airtight for as much as 60 cm of water overpressure in the ear canal relative to the middle ear. Underpressures are less tolerated. The weak pars flaccida explains the low rupture pressure for the tympanic membrane in Norwegian cattle (and in foxes). It is also possible that the pars flaccida is weakened

TABLE 1. RUPTURE PRESSURES OF MEMBRANES IN EARS FROM NORWEGIAN CATTLE

Ruptured	Rupture Pressure (atm)		Individual Results (atm)
	Mean	SD	
Tympanic membrane	0.39	0.17	0.170, 0.188, 0.210, 0.223, 0.243, 0.260, 0.263, 0.291, 0.303, 0.340, 0.342, 0.343, 0.345, 0.355, 0.355, 0.382, 0.397, 0.413, 0.418, 0.537, 0.543, 0.561, 0.563, 0.582, 0.792, 0.816
Reissner's membrane	0.047	0.017	0.0218, 0.0266, 0.0315, 0.0315, 0.0363, 0.0363, 0.0363, 0.0411, 0.0411, 0.0460, 0.0508, 0.0557, 0.0557, 0.0653, 0.0653, 0.0750, 0.0799
Round window membrane	>2.0		1.7, 1.7, 2.1, 2.1, >2.0, >2.0, >2.0, >2.0, >2.1, >2.2, >2.2, >2.2, >2.2, >2.3, >2.4
Oval window annular ligament	29.4	6.6	See Table 2

1 atm = 101.325 kPa = 10.33 m water = 1.033 kg/cm².

TABLE 2. FORCE AND PRESSURE AT STAPES FOOTPLATE THAT CAUSES ANNULAR LIGAMENT TO RUPTURE IN EARS FROM NORWEGIAN CATTLE

Ear	Oval Window Axes and Area			Rupture Force (kgf)	Rupture Pressure (atm)
	a (mm)	b (mm)	A (mm ²)		
1	2.320	1.440	2.624	0.543	20.0
2	2.470	1.505	2.920	0.590	19.6
3	1.860	1.270	1.855	0.600	31.3
4	2.223	1.095	1.912	0.600	30.4
5	1.760	1.180	1.631	0.600	35.6
6	2.240	1.240	2.182	0.610	27.1
7	2.125	1.360	2.270	0.610	26.0
8	2.370	1.550	2.885	0.626	21.0
9	2.260	1.310	2.325	0.640	26.6
10	2.340	1.340	2.463	0.645	25.4
11	2.385	1.375	2.576	0.726	27.3
12	2.320	1.305	2.378	0.742	30.2
13	2.120	1.380	2.298	0.750	31.6
14	2.310	1.180	2.141	0.800	36.2
15	2.000	1.210	1.901	0.838	42.7
16	2.100	1.430	2.359	0.940	38.6
Mean	2.20	1.32	2.30	0.68	29.4
SD	0.20	0.13	0.36	0.11	6.6

Applied force to footplate corresponds to pressure equal to force divided by area of oval window opening. This area is approximated by $A = \pi ab/4$, where a and b are axes of quasi-elliptical oval window opening. These axes are measured with x-y micrometer table, by displacing oval window in view field of microscope.

by the impulsive strain applied to it when the animal is slaughtered. In several ears, a hole in the pars flaccida was detected before the application of rupturing pressures.

To the author's knowledge, the rupture pressure of Reissner's membrane has not been measured before. It should be noted that this very thin membrane will leak after the ear bone has been frozen and thawed, possibly because of penetrating ice needles. The measurements should therefore be carried out on fresh and unfrozen temporal bones.

The round window membrane is normally very robust. Von Békésy⁸ reports that the human inner ear could bear a static pressure of about 4 atm before the bone began to drip. With special preparations of the round window, the round window membrane ruptured at static pressures of 4 to 7 atm. In the present study, the measurements were disturbed by leaks in the ear bone of Norwegian cattle at pressures of about 2 atm. Only slightly higher pressures were attainable. Two membranes ruptured at 1.7 atm of overpressure in the perilymph, and 2 at 2.1 atm. The other membranes did not rupture at the attainable pressures of at least 2 atm. In anesthetized cats, a much lower mean rupture pressure is reported for the round window membrane, 0.031 atm, with a standard deviation of 0.023 atm.⁷

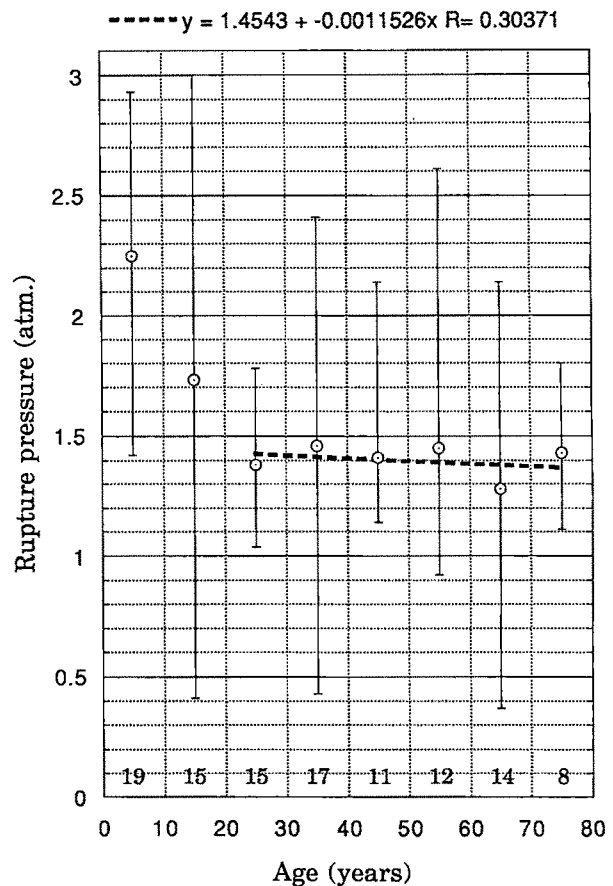


Fig 5. Rupture pressures of human tympanic membranes, according to Zalewski (1906).¹ Number of ears, mean rupture pressure, and range are indicated in each 10-year age interval.

According to von Békésy,⁸ the stapes is not visually affected by the maximum pressures that could be produced in the cochlea. He reports that the force necessary to tear it out by means of a hook is about 320 g, corresponding to a pressure of 16 atm applied to the footplate. These data seem to be inconsistent because they correspond to an area in the oval window of only 0.19 mm², while the mean area of the human footplate is about 3.2 mm².⁸ In the present study with ears from Norwegian cattle, the mean oval window area is 2.3 mm², the rupture force is 0.68 kgf, and the corresponding rupture pressure at the stapes is 29.4 atm. The whole pressure difference is supposed to be across the footplate, and only a negligible part of it across the round window membrane. The rupture force could not have been measured in the same way as von Békésy did. For Norwegian cattle, the crura of the stapes are too weak to withstand the needed drag force from a hook.

CONCLUSIONS

The rupture pressures of the tympanic membrane, Reissner's membrane, the round window membrane, and the annular ligament in the oval window have

all been measured in cadaver ears from Norwegian cattle (NRF). The rupture pressure of the tympanic membrane has also been measured in a few ears from foxes. Without exception, the ruptures of the tympanic membranes appear as small tears in the pars flaccida region, as opposed to in human ears, in which 99% of the ruptures are localized to the pars tensa.² The more vulnerable pars flaccida contributes to lower tympanic membrane rupture pressures than in human ears; the mean values are 0.39 atm for ears from Norwegian cattle and 0.59 atm for fox ears, as compared to about 1.4 atm for human ears above 20 years of age.

The static pressure difference that may be present across Reissner's membrane under real-life conditions, eg, in connection with Meniere's disease, is not

known to the author. But in ears from Norwegian cattle and for an increasing pressure difference, the membrane will be displaced and finally rupture at a mean overpressure in the endolymph of 0.047 atm, equivalent to 50 cm H₂O.

The round window membrane is very robust. On average, a static overpressure in the perilymph of more than 2 atm is usually needed to rupture it in Norwegian cattle, whereas von Békésy⁸ reports rupture pressures between 4 and 7 atm for human ears.

The annular ligament is even more robust. On average, rupture of the annular ligament in ears from Norwegian cattle occurs for an applied force to the stapes of 0.68 kilogram force, corresponding to a rupture pressure at the stapes of 29.4 atm.

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SENSITIVITY OF THE ENDOCOCCHLEAR POTENTIAL LEVEL TO COCHLEAR BLOOD FLOW DURING HYPOVENTILATION

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To study the relationship between endocochlear DC potential (EP) and cochlear blood flow (CoBF) under hypoxic conditions, we recorded the EP and CoBF from the basal turn of the cochlea in 21 guinea pigs. Hypoventilation for 10 minutes was induced by reducing the respiratory rate and volume. During hypoventilation, the EP declined in most of the cases to an intermediate level of the positive range in a few minutes. At the midpoint of the 10-minute hypoventilation, angiotensin II (5 μ g/kg or 1 mL/kg) was infused for 60 seconds to raise the systemic blood pressure. In this experimental manipulation of systemic blood pressure, the CoBF and EP generally rose transiently. We determined the sensitivity of the EP to a CoBF change (Δ) by calculating the $\Delta\text{EP}/\Delta\text{CoBF}$. More specifically, we analyzed the relationship between the $\Delta\text{EP}/\Delta\text{CoBF}$ and the EPi (EP level just before angiotensin II infusion). The ΔEP was equal to the maximum EP level after angiotensin II infusion minus the EPi . The ΔCoBF was equal to the maximum CoBF value after angiotensin II infusion minus the CoBF value just before infusion. The $\Delta\text{EP}/\Delta\text{CoBF}$ increased most in the range near 70% of the EPi . That is, the $\Delta\text{EP}/\Delta\text{CoBF}$ was greater and the EPi was lower in the range above 70% of the EPi . To elucidate this linear correlation in the range above 70% of the EPi , we must consider several factors. In the supplementary experiments for blood gas analysis using 11 guinea pigs, most of the data of the EPi in the range above 70% were found to be obtained under conditions of a PaO_2 of more than 12 mm Hg. As to the sensitivity increase of the EP to the ΔCoBF above mentioned, we propose that among several factors in the stria vascularis during hypoxemia, the activation of glycolysis in aerobic metabolism may be involved. As another possible factor, we postulate the increase in the reactive rate of the enzymatic activities that are linked with EP production and respond to the elevated cyclic adenosine monophosphate activity induced by the sympathicotonic state due to hypercapnia.

KEY WORDS — angiotensin II, cochlear blood flow, endocochlear DC potential, hypoventilation.

INTRODUCTION

An understanding of cochlear blood flow (CoBF) is of basic importance in the treatment of inner ear diseases. One of the principal roles of CoBF is the transport of O_2 to the inner ear tissues. An important factor in the regulation of regional blood flow is the CO_2 concentration in the capillaries, which is easily affected by changes in respiratory conditions.¹⁻⁴ Therefore, studies of the relationship between CoBF and cochlear function should be conducted under various respiratory conditions. In this study, we measured the CoBF in the lateral wall of the cochlea and recorded the endocochlear DC potential (EP) at the same site as a functional parameter of the stria vascularis. In this study of the relationship between the CoBF and the EP under hypoxic conditions, an intermediate level of EP was induced by hypoventilation, and its response to increased CoBF was observed. To raise the CoBF during hypoventilation, we increased the systemic blood pressure (BP) by the injection of angiotensin II into an external jugular vein. To analyze and discuss the obtained data in terms of blood gas changes, we performed a supplementary experiment to conduct a simultaneous blood gas analysis in an experiment the same as described above, but without angiotensin II infusion.

MATERIALS AND METHODS

Twenty-one healthy adult guinea pigs weighing 250 to 400 g were anesthetized with intraperitoneal pentobarbital sodium (30 mg/kg) and pancuronium bromide (0.1 mg/kg). Artificial respiration was maintained with a respirator (Harvard model 683) connected to a tracheotomy tube. The respiratory rate was initially set at 40 to 50 times per minute, and the tidal volume was 1 to 1.2 mL per 100 g of body weight. The body temperature was monitored by a rectal probe and maintained at about 38°C with a heating pad throughout the experiment. With the guinea pig in a dorsal position, the right cochlea was exposed through the auditory bulla. The electrode (a glass micropipette with a tip diameter of about 2 μ m, filled with 3-mol/L potassium chloride and connected to a microelectrode amplifier [Nihon Kohden MEZ-7200]) was placed on the thinned bony wall of the basal turn of the cochlea and advanced with a micro-manipulator through the stria vascularis and into the scala media. The indifferent electrode was placed on the exposed neck muscles. The endocochlear DC potential was monitored with an oscillograph (Kenwood CS 8010). A needle probe of a laser Doppler flowmeter (Medpacific LD 5000) was placed in the vicinity of the EP microelectrode with about a 2-mm dis-

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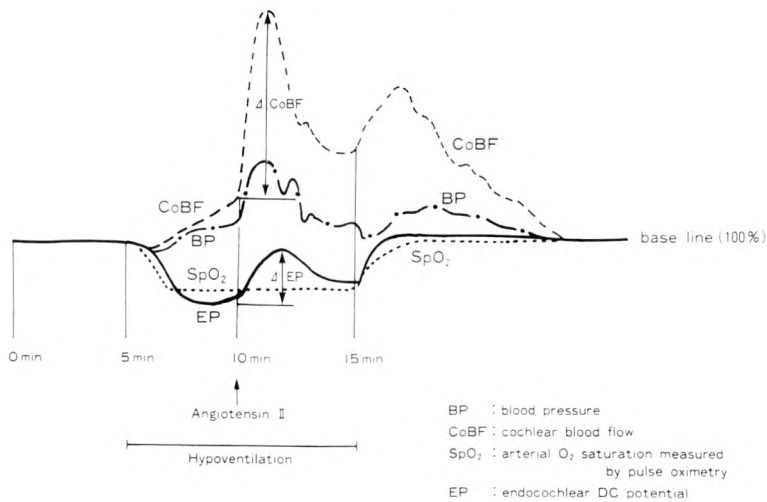


Fig 1. Schematic drawing shows results of hypoventilation experiment. Δ EP — maximum EP level after angiotensin II infusion minus EP level just before infusion (EPi); Δ CoBF — maximum CoBF value after angiotensin II infusion minus CoBF value just before infusion.

tance to the apical side.

The BP was recorded from either the femoral artery or the left common carotid artery by a pressure transducer (Nihon Kohden PT-200T). As a monitor of arterial O₂ saturation, a pulse oximeter was applied for the confirmation of hypoxemia during hypoventilation. The probe of the pulse oximeter (Nihon Kohden OLV-1100) was attached to the posterior footpad on the side not cannulated for BP recording. A 1-mL syringe connected to a tube placed in the left external jugular vein was used for the injection of angiotensin II. Hypoventilation (10 minutes) was induced by the reduction of the respiratory rate and volume to 40% to 60% of the initial set values. In animals that showed a slight decrease of EP during hypoventilation and maintained a stable BP after the first hypoventilation experiment, an identical second experiment was carried out after an interval of more than 20 minutes. We were able to obtain the data of 38 experiments from 21 guinea pigs. All data were

recorded on a pen recorder (Nihon Kohden WT-685), and samplings were made on a data recorder (TEAC DRF1) with a sampling frequency of 1 Hz. Changes in BP (millimeters of mercury), CoBF (relative value), and EP (millivolts) were converted by computer analysis to changes in percentage. The mean BP was calculated as the sum of 20 successive original BP data divided by 20.

As illustrated in Fig 1, in response to hypoventilation loading, the BP, CoBF, and EP generally showed some increases and/or decreases.⁵ At the point 5 minutes after the beginning of hypoventilation, angiotensin II (5 μ g/kg or 1 mL/kg in saline solution) was infused for 60 seconds to raise the EP. For the analysis of changes in CoBF and EP after angiotensin II infusion, we made the following definitions. The EPi was considered to be the EP level (millivolts) just before angiotensin II infusion (intermediate level of EP). The CoBFh was the CoBF value (relative value) just before angiotensin II infusion (CoBF value dur-

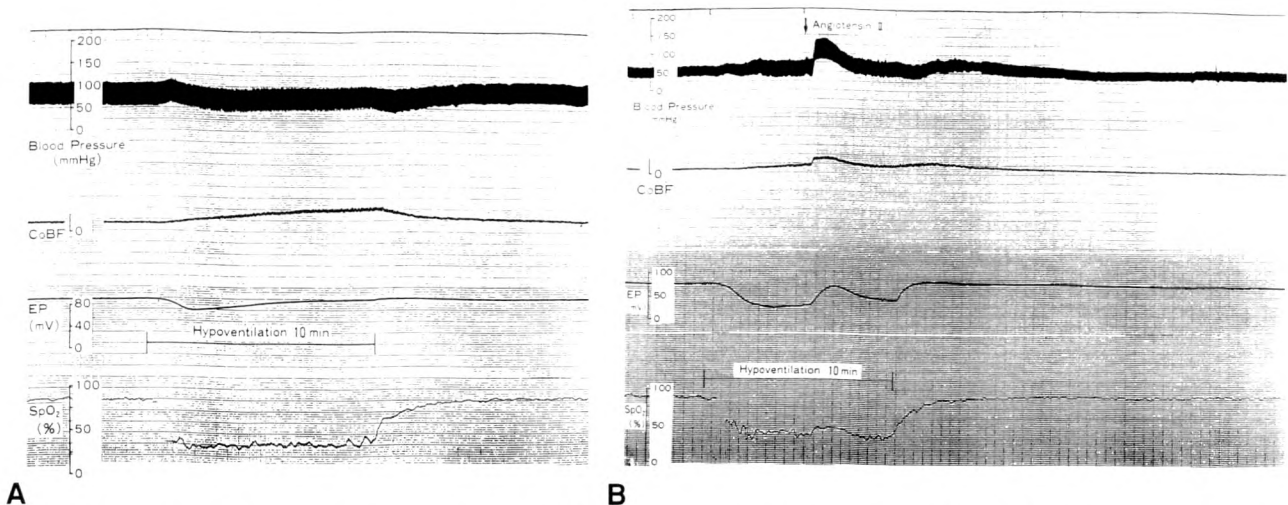


Fig 2. Recordings of hypoventilation experiment. A) Without angiotensin II infusion. Initial level of CoBF was 27 (relative value). B) With angiotensin II infusion. Initial level of CoBF was 17.

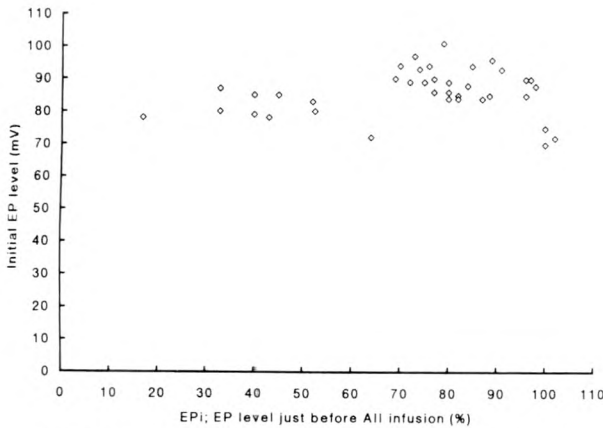


Fig 3. Distribution of EPI in relation to initial EP level. Note wider distribution of EPI. Angiotensin II.

ing hypoventilation). The change (Δ) in EP (Δ EP) was the maximum EP level (millivolts) after angiotensin II infusion minus the EPI. The Δ CoBF was the maximum CoBF value (relative value) after angiotensin II infusion minus the CoBFh.

As a supplementary experiment for simultaneous measurement of arterial blood gas during hypoventilation, another 11 healthy guinea pigs were used. During the same experimental procedure, except for angiotensin II infusion, 0.5 mL of arterial blood was drawn through the catheter cannulated into the left common carotid artery at 5 minutes after the start of hypoventilation. To observe the blood gas changes over the time course of hypoventilation, we obtained a second blood sample at 5 minutes after the first sample in 1 of the 11 animals. The blood samples were analyzed for P_{aO_2} and P_{aCO_2} .

RESULTS

Figure 2A illustrates the results of a single experiment, showing some changes that occurred during and after hypoventilation in the BP, CoBF, and EP. At the beginning of hypoventilation, the BP showed

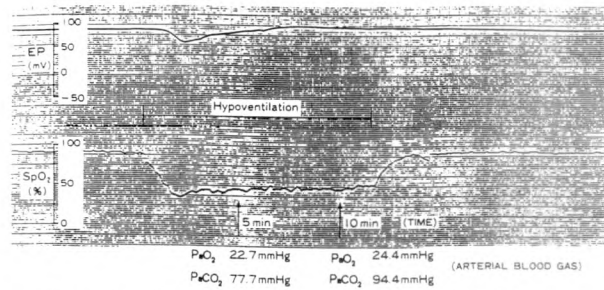


Fig 5. Results of arterial blood gas analysis at 2 points during hypoventilation in 1 animal, together with EP recording and arterial O_2 saturation monitoring (SpO_2). Note increase of P_{aCO_2} during hypoventilation.

a transient increase and then decreased slightly. The CoBF (initial value, 27) was found to increase gradually. In the analysis of the data of all experiments, the CoBF changes relative to the BP change that occurred during hypoventilation were divided into 3 types: 1) both the BP and the CoBF increased, 2) the CoBF increased while the BP decreased, and 3) both decreased. After the start of hypoventilation, the EP began to decline after a few minutes, remaining stable at a new, intermediate level that was dependent on the arterial O_2 saturation as measured by a pulse oximeter (SpO_2).⁵⁻⁸ Then, the EP continued to remain stable or increased or decreased gradually. Figure 2A shows an example of a gradual increase of EP.

Figure 2B demonstrates the changes in the EP of an animal with an angiotensin II-induced change in systemic BP and CoBF that occurred during and after hypoventilation. The BP was raised by an infusion of angiotensin II at the midpoint of the 10 minutes of hypoventilation. In response to the infusion, the systemic BP increased rapidly and then fell about 1 minute after the beginning of the angiotensin II infusion. The CoBF (initial value, 17) changed in parallel with the BP. The EP increased and decreased with a slower response than that of the BP or the CoBF. When the animal was returned to the initial

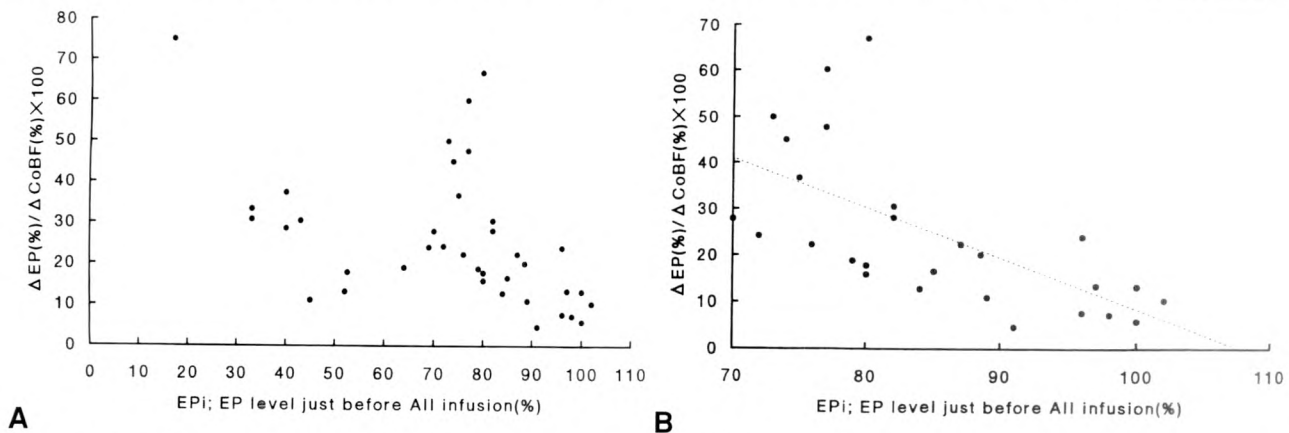


Fig 4. Correlations. A) Between $\Delta EP/\Delta CoBF$ and level of EPI ($n = 38$). B) Between $\Delta EP/\Delta CoBF$ and level of EPI in range of 70% to 110% of EPI with regression line ($n = 27$, $r = -.642$).

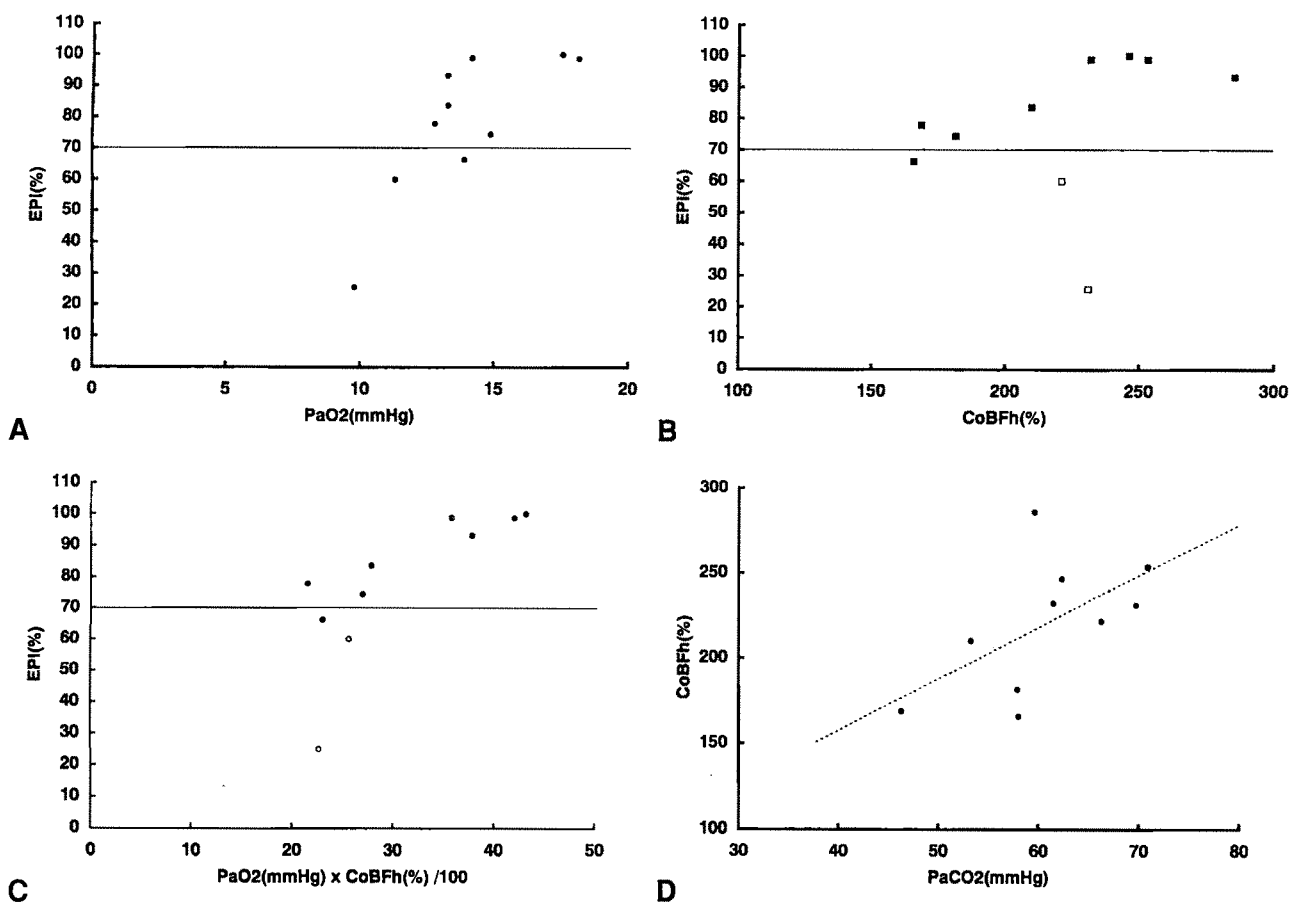


Fig 6. Results of supplementary experiment ($n = 10$). A) Relationship between EPI and PaO₂. Most of EPI data of more than 70% were found to be distributed in range above 12 mm Hg of PaO₂ value. B) Relationship between EPI and CoBFh during hypoventilation (CoBFh). Data were divided into 2 groups: data above 12 mm Hg of PaO₂ (filled squares), and data below 12 mm Hg of PaO₂ (empty squares). C) Relationship between EPI and value of PaO₂ times CoBFh. Data were divided into 2 groups: data above 12 mm Hg of PaO₂ (filled circles), and data below 12 mm Hg of PaO₂ (empty circles). D) Relationship between CoBFh and PaCO₂ with correlation coefficient of .579.

condition of ventilation, the EP generally proceeded to increase with an overshoot, then gradually returned to the baseline level.

Figure 3 shows the relationship between the initial EP level (millivolts) and the EPI (percent). Thirty-two of the 38 data of the initial EP level were distributed within the range from 77 to 96 mV, with the mean $\pm$ SD being 86.9 ± 4.88 mV. In contrast to the relatively narrow distribution of the initial EP level, the EPI was found to be distributed in a wider range, from 17% to 102%. Most of the data of the initial EP level above 82 mV showed a predilection for a range in EPI of more than 69% and less than 98%.

All data obtained were analyzed for the ratio $\Delta EP / \Delta CoBF$. Figure 4A shows the relationship between the $\Delta EP / \Delta CoBF$ and the EP level just before the angiotensin II infusion (EPI). The value of the $\Delta EP / \Delta CoBF$ rose as the EPI decreased in the range of 70% to 110% (of the EPI). Below 70% of the EPI, there was no significant relationship between them; the $\Delta EP / \Delta CoBF$ decreased as the EPI decreased in the

range between 70% and 45% (of the EPI). Figure 4B shows the correlation between them from 70% to 110% of the EPI with a regression line. A negative correlation was clearly demonstrated with a correlation coefficient of .642.

Figure 5 shows the results of arterial blood gas analysis at 2 points during hypoventilation in 1 animal, together with EP recording and SpO₂ monitoring. The PaO₂ changed very little, but the PaCO₂ showed an appreciable increase in the 5-minute interval. The EP initially decreased in parallel with the SpO₂ to a bottom-line level, then increased gradually to a transient rise above baseline, although the SpO₂ remained low and stable. After normal ventilation was restored, both the EP and SpO₂ returned to baseline.

Figure 6A shows the results of the supplementary experiment, showing the relationship between the EPI and the PaO₂. As shown here, most of the EPI data of more than 70% were found to be distributed in the range above 12 mm Hg of the PaO₂ value. Figure 6B

illustrates the relationship between the EPi and the CoBFh. As shown in the graph, the data were divided into 2 groups: data above 12 mm Hg of PaO₂ and data below 12 mm Hg of PaO₂. The former were distributed mostly in the range above 70% of the EPi. In this range, the EPi increased as the CoBFh rose, reaching 100% when the CoBFh rose more than 230%, despite the hypoxemic condition. In Fig 6C, the horizontal axis represents the product of the PaO₂ and the CoBFh (percent) as a function of O₂ transport to the cochlear tissue. The relationship of this product with the EPi value showed a similar relationship of PaO₂ with the EPi value (Fig 6A) in that the level of the EPi rises as the product of the PaO₂ and the CoBFh increases in the data above 12 mm Hg of PaO₂. As shown in Fig 6D, the data of the CoBFh were found to be generally in a positive correlation with those of the PaCO₂, demonstrating the corresponding increase of the CoBFh in the condition of hypercapnia (45 mm Hg < PaCO₂ < 75 mm Hg). Thus, the EPi data of more than 70% were characterized as the data for which the PaO₂ value was above 12 mm Hg. Such data were demonstrated to be CoBFh-dependent (Fig 6B). As stated above, these CoBFh values showed a correlation with those of the PaCO₂ to a lesser degree.

DISCUSSION

As is well known, a physiological oxygen supply to the stria vascularis is needed to maintain a normal EP level. In anoxic animal experiments, the EP falls from its normal positive value to a negative value a few minutes after the onset of anoxia.⁹⁻¹¹ The stria vascularis is considered to be responsible for the energy source of the EP.¹² Therefore, it is important to record the EP and CoBF simultaneously in the lateral wall of the cochlea.

In the present study, we analyzed the sensitivity of the EP to an increase of CoBF induced by angiotensin II in relation to the EPi level. The ratio of the Δ EP to the Δ CoBF rose as the EPi level decreased in the range of EPi from 70% to 110%. The major factors in the stria vascularis that maintain EP levels in the positive range are generally thought to be local blood flow, O₂ delivery, O₂ utilization, intracellular function, etc.¹³ Therefore, changes in the Δ EP/ Δ CoBF reflect changes in O₂ delivery, O₂ utilization, or intracellular function. An early study suggested that carbonic anhydrase in the stria vascularis could be activated by hypercapnia to affect the generation of the EP.¹⁻³ This would involve changes of intracellular function in the stria vascularis.

Although Quirk et al,¹⁴ in a study using normal rats, suggested the presence of angiotensin II receptor in the cochlear blood vessels, it has not been stud-

ied whether an angiotensin II receptor is present in the cochlear blood vessels in guinea pigs. According to our earlier study using guinea pigs, CoBF showed a parallel increased pattern depending on the BP increase by angiotensin II injection, while skin blood flow in the auricle of the same side decreased to a level below the initial level.¹⁵ This may indicate that the direct effect of angiotensin II on cochlear blood vessels is slight even if an angiotensin II receptor is present. In the present study, a sharp increase of BP after angiotensin II infusion caused a concomitant rise in CoBF, which might increase O₂ permeability in the cochlear capillaries.¹⁶ This could be one of the factors in increasing the sensitivity of the EP to a Δ CoBF.

The mechanism by which the sensitivity of the EP to the CoBF increase rises maximally in the range near 70% of the EPi is not yet clear. In this range, glycolysis in the stria vascularis could be activated to produce more biochemical energy for EP generation. In brain tissue, ischemia has been shown to increase glycolysis rates at least fourfold to sevenfold in different experimental groups of mice.¹⁷ In the present experiment, the data of EPi of more than 70% were obtained exclusively when the values of the PaO₂ were more than 12 mm Hg and when the initial values of the EP were more than 82 mV (Figs 3 and 6A). From the viewpoint of the PaCO₂, the condition of hypercapnia during hypoventilation (45 mm Hg < PaCO₂ < 75 mm Hg; Fig 6D) may induce a sympathicotonic state with the elevation of serum epinephrine levels.⁴ Because a higher level of epinephrine causes production of more cyclic adenosine monophosphate (AMP) in various parts of the body, the enzymatic activities that generate the EP could be increased in reaction rate.¹⁸⁻²⁰ This activated enzymatic reaction in the stria vascularis is thought to be sustained by the above-mentioned activated glycolysis as its energy resource, if the PaO₂ level remains more than 12 mm Hg. Thus, the range near 70% of the EPi can be regarded as being a critical range in altering the enzymatic activity in the rate-limiting step of the metabolism in the stria vascularis. However, we could not elaborate on the finding that the Δ EP/ Δ CoBF decreased as the EPi increased from 70% to 110%. There exists the possibility that in saturated levels of the EP near 100%, the EPi is not increased to a greater extent by a CoBF increase, compared with the lower range from 80% to 70%.

In the above-mentioned conditions of arterial blood gas (12 mm Hg < PaO₂; Fig 6A), the EPi was found to increase as the CoBF increased (Fig 6B). As shown in Fig 5, the PaCO₂ rises as the time of hypoventilation proceeds. This induces the increase

of CoBF so that there may occur the gradual increase of an intermediate level of EP (Fig 2A). This implies that the CoBF increase induced by the PaCO₂ increase (Fig 6D) promotes O₂ transport to the inner ear tissue if the PaO₂ is above a certain level (Fig 6C).^{2,3}

Although, in the present study, the EP recording during hypoventilation showed 3 patterns: a stable pattern, a gradually increasing pattern, and a gradually decreasing pattern, its level did not decrease substantially, remaining within the positive range. In such hypoxemic conditions still sustaining the EP level within the positive range, the rate of energy use could be kept lower, even though ample carbohydrate reserves or adenosine triphosphate may still be available. Lowry et al¹⁷ suggest that such a decrease of energy expenditure may represent a self-regulated protective measure geared to a more economical use of the remaining resources. In some individuals, however, the EPi in the range from 30% to 40% responds moderately to the CoBF increase (Fig 4A). This may reflect a corresponding energy use for EP production in the stria vascularis, in which restoration of biochemical reserves takes place during a CoBF increase.

In general, hypercapnia induces vasodilatation and activates the autonomic nervous system to increase the plasma concentrations of epinephrine and norepinephrine, leading to an increase of cardiac output, elevation of the BP, and a decrease of peripheral vascular resistance. These changes may also occur in the microcirculation of the cochlear blood vessels. On the other hand, hypoxia and hypercapnia induce di-

rectly, in contrast to the stimulating effects mentioned above, suppression of cardiac activity. In the present study, the changes in CoBF caused by hypoventilation were of 3 types in relation to the BP. In 1 type, the CoBF increased while the BP decreased. Such an increase of CoBF during hypoventilation, which occurred in most of the animals in the present study, can be regarded as the result of mutual effects of hypoxia, hypercapnia, and anesthesia.^{1,21} The supplementary experiment demonstrated that the CoBF increases as the PaCO₂ level rises. Therefore, hypercapnia could be one of the potentiating factors in the CoBF increase that occurs during hypoventilation.

As a significant finding of the present study, we stated that the $\Delta EP/\Delta CoBF$ increased most in the range near 70% of the EPi. Concerning this finding, we described some elucidations, including a sharp increase of CoBF by angiotensin, activation of glycolysis in the stria vascularis, and an increase of the biochemical reaction rate by cyclic AMP in EP generation. Although it would be very difficult to explain the above findings by more subtle mechanisms, the insight into the EP changes that occur during hypoventilation should be deepened by considering further other biological processes, such as changes of carbonic anhydrase activity in the stria vascularis and changes of electrical resistance in the cochlear compartment. We should also discuss the significance of the clinical implication that if the intermediate level of EP during hypoventilation remains above 70% of its initial level, the *in vivo* condition provides the possibility of returning the EP to the initial level.

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UNILATERAL NASAL NITRIC OXIDE MEASUREMENT AFTER NASAL SURGERY

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This study was designed to validate and standardize a method for unilateral nasal nitric oxide (NO) measurement. Fourteen healthy volunteers and 11 patients who had undergone unilateral medial maxillectomy were enrolled. Nasal NO was measured unilaterally by means of a dual pump system, and bilateral nasal NO was measured by aspirating air through the nasal airway in series. The median unilateral NO output was 195 nL/min on the surgical side and 291 nL/min on the contralateral, surgically untreated side ($p = .006$). The NO output was not significantly different between nostrils in the control group ($p = .82$). With the bilateral technique, there was no significant difference between the surgery group and the healthy-subjects group ($p = .72$). The unilateral nasal NO technique is sensitive in determining unilateral differences in nasal NO production. The NO outputs from the nostrils were similar in normal subjects regardless of the nasal cycle, but were significantly lower on the operated side in the unilateral nasal surgery group.

KEY WORDS — nasal nitric oxide, unilateral measurement.

INTRODUCTION

The ability of mammalian cells to synthesize an endothelially derived relaxant factor (EDRF) was first demonstrated by Furchgott and Zawadzki¹ in 1980. Subsequent investigations have shown that the actions of EDRF and nitric oxide (NO) were substantially similar.^{2,3}

Nitric oxide is produced in human airways by NO synthases using the amino acid L-arginine as substrate.⁴

It has been suggested that NO is an important intercellular and intracellular mediator, governing several physiological functions in animals and humans. The functions range from control of smooth muscle tone in the cardiovascular, gastrointestinal, respiratory, and genitourinary systems to neurotransmission and a role in immune function and inflammation.⁵

Nasal NO was first detected by Alving et al⁶ in 1993, and since then, extensive reports on the origins, functions, and measurement of nasal NO have been published.⁵ Nasal NO plays an active role in the physiological and pathological processes of respiratory and nasal airways. These processes include modulation of pulmonary and systemic vascular tone,^{7,8} regulation of ciliary function,⁹ and maintenance of a sterile environment in the nasal airways

and sinuses.¹⁰ It has been demonstrated that nasal NO is increased in patients with allergic rhinitis¹¹ and decreased in children with Kartagener's syndrome, cystic fibrosis,¹²⁻¹⁴ and acute or chronic sinusitis.^{4,15} The decrease in NO levels caused by the use of corticosteroids implies that nasal NO can be a potentially useful marker of nasal airway inflammation and immune response.¹⁰

Several techniques for total nasal airway NO measurement have been described,¹⁶⁻²¹ but a method for unilateral nasal NO measurement has not yet been well established.

We hypothesized that nasal NO levels might be changed after nasal surgery because of the alteration of the nasal mucosa. The aim of this study was to validate a unilateral nasal NO measurement technique by determining the ability to detect differences in NO levels between the nasal passages of patients who had undergone unilateral medial maxillectomy. The aspiration flow, as well as the manipulation of breathing patterns, was standardized.

METHODS AND MATERIALS

Fourteen healthy volunteers (age range, 19 to 48 years; age mean, 34.2 ± 8.7 years; 12 men and 2 women) and 11 patients who had undergone unilat-

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eral medial maxillectomy through a lateral rhinotomy (age range, 38 to 73 years; age mean, 60.8 ± 14.2 years; 10 men and 1 woman) were recruited for this study. The pathological diagnosis in the surgical group was inverting papillomatosis in 10 patients and plasmacytoma in 1 patient. The length of the postoperative period at the time of assessment ranged from 3 to 10 years. The subjects had no history of a recent upper airway tract infection or allergy. All were non-smokers. All subjects provided informed consent. The study was approved by the Human Ethics Committee of the University of Toronto.

NASAL VOLUME MEASUREMENT

The nasal cavity volume was determined by an acoustic rhinometer (Rhin2100, Rhinometrics A/S, Lyngby, Denmark, software version 1.29) before each NO measurement. Three independent traces with less than 5% variation of the maximum cross-sectional area (MCA) were accepted. The average volumes was calculated over a distance of 2 to 5 cm measured from the nostril.²²

NITRIC OXIDE MEASUREMENT AND SAMPLING TECHNIQUES

Nitric oxide was measured by a rapid-response chemiluminescent NO analyzer (Sievers 280, Boulder, Colo). The sampling flow of the vacuum pump was 0.2 L/min. A daily 2-point calibration was performed, first with 100% nitrogen to zero, then with an analyzed standard gas (NO 1.6 ppm, Praxair, Mississauga, Canada) for the span. The zero and span measures were checked periodically throughout testing. The NO analyzer signal output was fed to a computer data acquisition program (DasyLab for Windows, DasyTec Corp, Amherst, NH) with a real-time chart recorder-like display of NO versus time written directly to the computer's hard disk as a data file. The NO concentrations were measured with a data analysis program written in-house (Microsoft Visual Basic).

NASAL NITRIC OXIDE MEASUREMENT

The ambient NO concentrations were recorded before and after each measurement and were used to correct the measured nasal NO concentrations. In most of the cases, the aspiration flow varied between 3 and 6 L/min according to the nasal volume previously measured by acoustic rhinometry. If the unilateral nasal volume was equal to or less than 2 mL, a flow of 3 L/min was selected. If it was larger than 2 mL, a flow of 6 L/min was used. The congested side of the nose was usually measured first, so that we could begin with lower flows. This was a more comfortable start for the subjects that allowed them to become accustomed to the higher flows needed for

the more patent nasal cavity. The nasal NO concentration was recorded as the mean of 3 consecutive measurements.

Unilateral Nasal Airway NO Measurement (Nasal Cavities Measured in Parallel). Two nozzles connected to 2 separate pumps were positioned in the nostrils. The subject was instructed to breathe tidally through the mouth for 1 minute during each measurement. This dual pump system enabled air to be aspirated concurrently but separately from each nasal cavity and replaced by room air via the open mouth. A side-arm sampling tube was attached to 1 nozzle, allowing NO measurement from 1 nostril for each maneuver. The mean of the NO peak concentrations of the last 5 breaths in each measurement was recorded.

In a previous preliminary study, healthy subjects were instructed to breathe through the mouth using different breathing patterns (breath-holding, tidal breathing, slow breath, and rapid breath) while air was aspirated from the nostrils by the dual pump system described above. The aim of this pretest was to determine whether unilateral NO measurements were affected by the breathing pattern.

Bilateral Nasal Airway NO Measurement (Nasal Cavities Measured in Series). To determine the total nasal airway NO, a nozzle connected to an adjustable pump was positioned in 1 nostril and the NO sampling tube was connected via a side-arm to the nozzle. The subject was instructed to take a deep inspiration and then blow against a mouthpiece fitted with a fixed resistor in order to close the nasopharyngeal velum, avoiding contamination from the lower airways. Room air was sucked from 1 nostril via the nasopharynx to the opposite nostril. A steady plateau of NO concentration was defined by a variation of less than 5 ppb over a period of at least 10 seconds.

A subgroup of the enrolled volunteers ($n = 5$) was used to determine the interday reproducibility of these techniques. Both nasal NO measurements were repeated daily for 1 week.

The nasal NO output (in nanoliters per minute) was calculated as the product of NO concentration (in parts per billion or nanoliters per liter) and minute ventilation (in liters per minute).¹⁶

Statistical analysis was conducted with the Wilcoxon rank test. Values were given as medians and quartiles (Q1, Q3). The reproducibility of the techniques for unilateral and bilateral nasal NO measurements and the agreement between interday measurements were assessed by the ANOVA test. The reproducibility was also determined as the coefficient of varia-

TABLE 1. NASAL VOLUMES AND NASAL NITRIC OXIDE OUTPUTS IN SURGERY GROUP

Patient No.	Treated Side		Unilateral Method Untreated Side		Sum		Bilateral Method
	Volume	NO	Volume	NO	Volume	NO	NO
1	3.0	477.0	1.4	1,050.0	4.4	1,527.0	1,122.0
2	6.5	252.0	1.7	450.0	8.3	702.0	492.0
3	10.0	195.0	4.5	252.0	14.5	447.0	342.0
4	6.1	216.0	4.9	366.0	11.0	582.0	465.5
5	6.8	216.0	3.8	252.0	10.6	468.0	366.0
6	14.7	63.0	3.2	238.0	17.9	301.0	444.0
7	5.1	305.0	3.5	440.0	8.6	745.0	825.0
8	2.5	161.2	2.3	291.0	4.8	452.2	436.0
9	6.5	154.2	3.4	285.0	9.9	439.2	438.6
10	5.0	138.0	5.5	432.0	10.5	570.0	595.0
11	6.7	72.0	2.5	264.0	9.2	336.0	287.0
Median	6.5	195.0	3.3	291.0	9.9	468.0	444.0
Q1	5.3	146.1	2.4	258.0	8.4	443.1	401.01
Q3	6.8	234.0	4.3	436.0	10.8	642.0	543.5

Volume — nasal cavity volume in milliliters; NO — nasal nitric oxide output in nanoliters per minute; Q1, Q3 — quartiles.

tion. Statistical significance was considered to be present when $p < .05$. GraphPad Prism (Version 2.01) was used for statistical analysis.

RESULTS

The median (Q1, Q3) nasal NO output in the surgical group was 195 (146.1, 234) nL/min in the operated side and 291 (258, 436) nL/min in the surgically untreated side ($p = .006$). The median (Q1, Q3) nasal volume was 6.5 (5.3, 6.8) mL in the operated side and 3.3 (2.4, 4.3) mL in the opposite side ($p = .007$; Table 1 and Fig 1). In the healthy-subjects group, the median (Q1, Q3) nasal NO output was 261 (203.3, 315.8) nL/min in the nasal cycle congested side and 258 (192, 293.3) nL/min in the nasal cycle ventilated side ($p = .82$). The nasal volume was 2.1 (2, 2.3) mL in the cycle congested side and 2.9 (2.8, 3) mL in the ventilated side ($p = .0001$; Table 2 and Fig 2).

There was no significant difference in total nasal NO output between the surgery group and the healthy

group via the bilateral technique ($p = .72$). There was also no significant difference in NO output measured by the bilateral technique and the sum of unilateral NO outputs in both the surgery group ($p = .18$) and the healthy subjects ($p = .64$).

The unilateral nasal NO peak concentrations were stable for different breathing patterns during mouth breathing under sufficient aspiration flow (Fig 3A). Insufficient aspiration flow resulted in a continued increase in the peak NO concentration (Fig 3B).

The ANOVA test showed no significant interday difference in either unilateral or bilateral nasal NO measurements. The reproducibility was high for both techniques (coefficient of variation $< 6\%$).

DISCUSSION

The method for unilateral nasal NO measurement described in this paper differs from that of other reports, in that 2 pumps were used simultaneously, each connected to its own rotameter. Hence, the flow

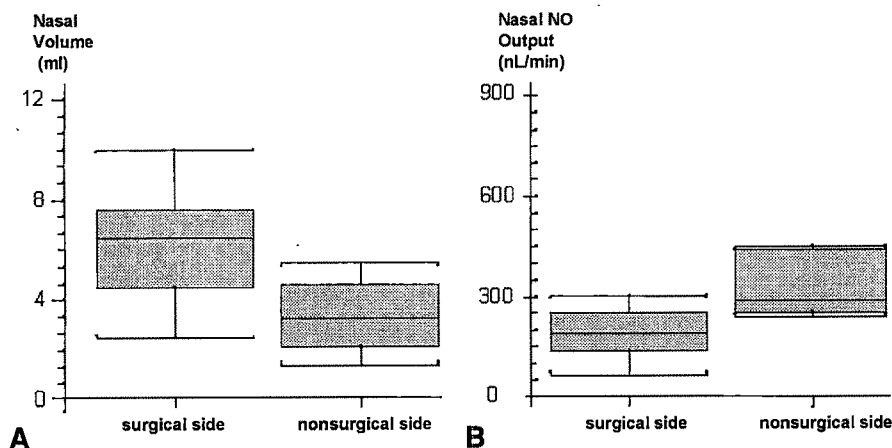


Fig 1. Unilateral nasal cavity volume and nasal nitric oxide (NO) output in surgery group. A) Nasal volume on operated and nonoperated sides ($p = .012$). B) Nasal NO output on operated and nonoperated sides ($p = .006$).

TABLE 2. NASAL VOLUMES AND NASAL NITRIC OXIDE OUTPUTS IN CONTROL GROUP

Subject No.	Congested Side		Unilateral Method Ventilated Side		Sum		Bilateral Method
	Volume	NO	Volume	NO	Volume	NO	NO
1	1.9	174.8	2.2	163.2	4.1	338.0	322.5
2	2.1	258.0	2.3	270.0	4.4	528.0	520.0
3	1.3	130.9	2.4	129.3	3.8	260.2	244.3
4	1.6	126.6	2.9	136.9	4.5	263.5	260.1
5	2.3	264.0	3.0	273.0	5.3	537.0	594.0
6	2.6	201.0	3.0	294.0	5.6	495.0	528.0
7	2.0	318.0	3.3	201.0	5.3	519.0	468.0
8	2.3	291.0	2.7	291.0	5.0	582.0	558.0
9	2.4	324.0	2.9	324.0	5.3	648.0	666.0
10	2.7	309.0	3.0	246.0	5.7	555.0	684.0
11	2.0	369.0	2.9	366.0	4.9	735.0	612.0
12	2.1	249.0	2.9	207.0	5.0	456.0	450.0
13	2.0	210.0	2.9	189.0	4.9	399.0	350.0
14	2.3	360.0	3.6	372.0	5.9	732.0	686.0
Median	2.1	261.0	2.9	258.0	5.0	523.5	524.0
Q1	2.0	203.3	2.8	192.0	4.6	413.3	375.0
Q3	2.3	315.8	3.0	293.3	5.3	575.3	607.5

through each nasal cavity was known and could be adjusted individually to achieve a maximum NO output through both sides at the same time. The development of an accurate, reproducible, and easy-to-apply method for unilateral nasal NO measurement may give important information in certain clinical situations, as in the evaluation and monitoring of unilateral nasal lesions.

This study demonstrated a significant difference of unilateral NO between the operated and nonoperated sides ($p = .006$), whereas there was no difference in healthy subjects between the nostrils ($p = .82$). However, with the bilateral technique, no significant difference in total nasal airway NO output

was found between the surgery group and the healthy group ($p = .72$). The unilateral method permits detection of differences in NO levels between the 2 nostrils. This situation has not been described previously. It might also be useful in the comparison of nasal responses to challenges by factors that might affect nasal NO values.

The medial maxillectomy performed in the surgical group caused a decrease in nasal mucosa surface area and better ventilation between the maxillary sinus and the nasal airway. This was probably due to loss of the considerable epithelial surface area of the turbinates, coupled with stripping of the maxilla during removal of the inverting papillomatosis. Scarring

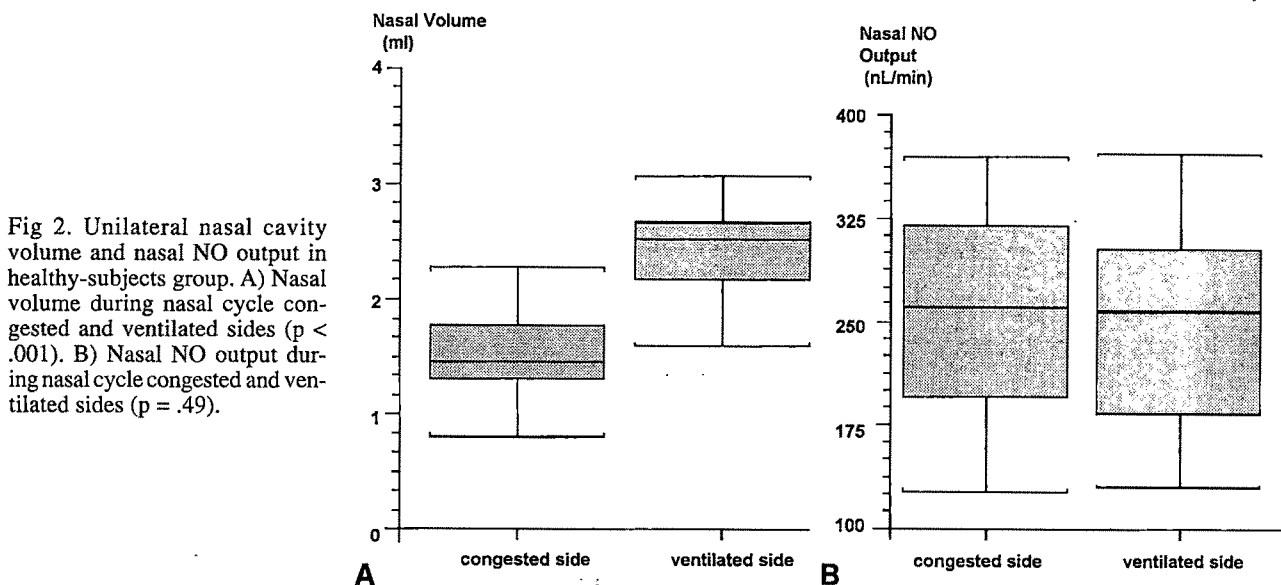


Fig 2. Unilateral nasal cavity volume and nasal NO output in healthy-subjects group. A) Nasal volume during nasal cycle congested and ventilated sides ($p < .001$). B) Nasal NO output during nasal cycle congested and ventilated sides ($p = .49$).

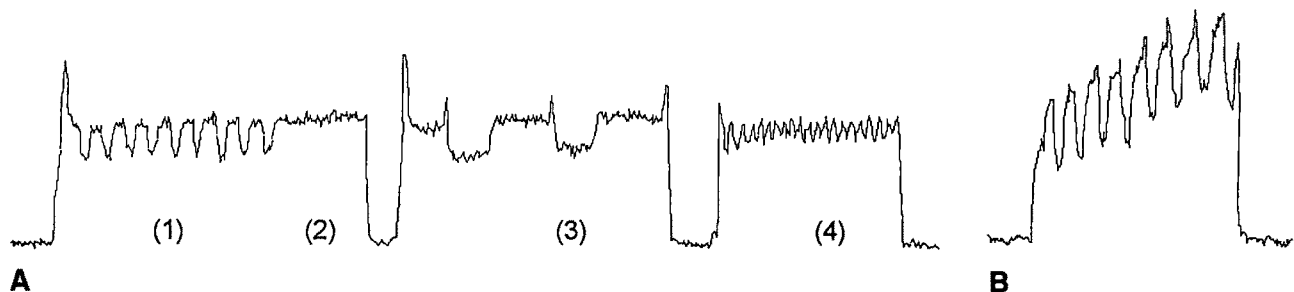


Fig 3. Effect of oral breathing pattern and aspiration flow on unilateral nasal NO concentration. A) Nasal NO peak values are unchanged. Flow rate is 6 L/min. (1) — Tidal breathing; (2) — breath-holding; (3) — slow breathing; (4) — rapid breathing. B) Nasal NO peak concentration fails to reach stable state at low flows. Flow rate is 2 L/min.

and diminished blood flow may play a part, too. Considering that the sum of NO from the nostrils and the bilateral nasal NO were not significantly different between the groups, we may speculate that an adaptation occurred in the NO production on the surgically untreated side. Further studies are necessary to explore these observations.

Confirming previous observations,²² the present study showed that in order to achieve maximum NO output, it is necessary to adjust the aspiration flow to the subject's nasal volume. If the aspiration flow is low, the flow profile through the nasal cavity may be predominantly laminar, in contrast to higher flows. An aspiration flow with more laminar characteristics would tend to insulate the mucosa from the mainstream and scrub NO less effectively from the mucosal surface.²³

Although the nasal volume measurements obtained by acoustic rhinometry were useful in selecting a suitable aspiration flow, it is not essential to evaluate the nasal volume before NO measurement in clinical applications. The profile of the NO peak concentrations is a reliable guide for the adequacy of the aspiration flow. When the aspiration flow is sufficiently high, the nasal NO peak concentrations at each breath are reproducible during mouth breathing (variation less than 5 ppb). A sequence of NO peaks that is constantly rising during measurement indicates that the flow is insufficient (Fig 3B). In the surgical group, some subjects, whose nasal cavities were particularly large on the operated side, needed flows as high as 7 or 8 L/min to reach a stable NO measurement. However, when the aspiration flow is too high, it may in-

duce velopharyngeal orifice closure, with attendant discomfort to the subject and failure of the NO measurement. In this study, we found that for most subjects the optimal range of unilateral aspiration flow was between 3 and 6 L/min.

Among the healthy volunteers, the nasal NO output was similar in both nostrils. Also, there was no relationship between the unilateral NO output and the nasal cyclical changes. This finding confirmed that nasal NO output is independent of nasal volume changes when measured at high flows, as has been demonstrated by Chatkin et al.²²

SUMMARY

1. The unilateral nasal NO measurement technique is sensitive in determining unilateral differences in nasal NO production and may be useful in clinical and research applications.
2. The unilateral technique is comfortable and easily performed. It also has good reproducibility.
3. It is important to select a suitable aspiration flow for each nostril. In this study, the optimal range of aspiration flow was between 3 and 6 L/min for most subjects.
4. In normal subjects, the unilateral nasal NO output is similar in both nostrils and is independent of the cyclical changes in nasal volume. After unilateral nasal surgery, the NO output on the operated side is lower than that on the nonoperated side, even after appropriate adjustment of flow. Further studies are necessary to explain these findings.

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STIMULATION OF ADENOIDAL LYMPHOCYTES BY *ALLOIOCOCCUS OTITIDIS*

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Otitis media with effusion (OME) is characterized by persistent effusion in the middle ear cavity and by chronic inflammation in the middle ear mucosa. *Alloiococcus otitidis*, a gram-positive aerobic bacterium, has been isolated in middle ear effusion, and by means of sensitive polymerase chain reaction detection assays it has been detected in as many as 20% of middle ear aspirates of patients with OME. Because *A otitidis* may freely interact with leukocytes in the middle ear effusion, it may potentially modulate the inflammatory reaction in OME. To study the nature of these interactions, we applied an in vitro assay in which killed *A otitidis* bacteria were incubated with peripheral blood and adenoidal mononuclear cells. The expression of the proliferation-associated surface marker CD69 was then measured in B lymphocytes and in CD4+ helper and CD8+ cytotoxic-suppressor T lymphocytes by means of multicolor flow cytometry. *Alloiococcus otitidis* induced the expression of CD69 in both peripheral blood and adenoidal T and B cells. Among the T cells, the cytotoxic-suppressor T lymphocytes were preferentially activated. It was also tested whether *A otitidis* would have an effect in another cytotoxic and immunoregulatory system, namely, the induction of natural killer cell activity in peripheral blood mononuclear cells. However, the effect was minimal compared with that of *Salmonella minnesota* or *Staphylococcus aureus*. The results show that *A otitidis* has a unique immunostimulatory capacity in vitro that is mainly confined to CD8+ T lymphocytes.

KEY WORDS — *Alloiococcus otitidis*, otitis media.

INTRODUCTION

Otitis media with effusion (OME) is characterized by chronic inflammation in the middle ear mucosa with accumulation of fluid in the middle ear cavity. Routine bacterial cultures of middle ear effusion (MEE) have yielded bacterial growth in only 20% to 30% of patients with OME.¹ With more sophisticated methods, such as polymerase chain reaction (PCR), the detection rate could be increased as much as 90%.²⁻⁵ The pathogenic bacteria most often encountered include *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.

Alloiococcus otitidis is a gram-positive bacterium that was first described as an intracellular pathogen associated with OME.⁶ In a recent study in which PCR was applied for the detection of microbes, *A otitidis* was found in 20% of MEE samples, either alone or in combination with *H influenzae*⁵ (and in certain child cohorts in as many as 40% of MEE samples; P. Hendolin, personal communication, 1999). This finding raises the possibility that *A otitidis* may have a pathogenic role in OME. To address the question more closely, we analyzed the capacity of *A otitidis* to activate peripheral blood and adenoidal lymphocytes in vitro as measured by the induction of expression of the early lymphocyte activation antigen CD69⁷ after contact with *A otitidis*.

MATERIALS AND METHODS

Lymphocyte Isolation and Culture Conditions. Human peripheral blood from healthy donors was obtained from the Finnish Red Cross Blood Bank (Helsinki, Finland). Adenoid tissue was obtained from children who underwent adenoidectomy at the Department of Otorhinolaryngology at the Helsinki University Central Hospital. All patients underwent operation because of recurrent otitis media and had more than 6 previous episodes of otitis media. The mean age of the patients was 3.2 years (range, 2.1 to 4.5 years). The operation was performed with the patient under general anesthesia. The epipharynx was inspected visually by means of traction on the velum and a mirror. The adenoids were removed by means of a round operation knife under visual control. Removed adenoids were immediately transferred to the laboratory on ice. The adenoid tissue was minced with scissors and passed through a fine wire mesh to obtain a single-cell suspension.

The mononuclear cells were separated by Ficoll/

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Hypaque centrifugation to remove dead cells. After washing, the cells were suspended in growth medium RPMI 1640 (Whittaker MA Bioproducts; Walkersville, Md) supplemented with 1-mmol/L glutamine (Gibco Laboratories; Chagrin Falls, Ohio), antibiotics (penicillin 100 U/mL and streptomycin sulfate 100 µg/mL, Gibco), and 2.5% human blood group AB serum (Finnish Red Cross Blood Service, Helsinki, Finland) at a cell concentration of 2.5×10^6 /mL.

Stimulation of Lymphocytes by Bacterial Contact. The *A. otitidis* used was American Type Culture Collection (ATCC) strain 51267. Formalin-fixed *Staphylococcus aureus* was purchased from Sigma (St Louis, Mo). The glutaraldehyde-fixed *Salmonella minnesota* strain mR595 bacterium used in this study was a rough (Re) mutant lacking the O-polysaccharide and containing only the innermost ketodeoxyoctonate-oligosaccharide of lipopolysaccharide. In brief, peripheral blood mononuclear cells (2.5×10^6 /mL) were incubated with bacteria at a lymphocyte-to-bacteria ratio of 1:2 for 12 to 18 hours in RPMI 1640, were washed once, and were assayed for CD69 expression or cytotoxicity.⁸ A bacterial cell wall component, lipoteichoic acid (LTA) from *Streptococcus pyogenes*, was used to stimulate immune cells at concentrations of 5 to 10 µg/mL (Sigma).

Antibodies and Flow Cytometry. Isolated peripheral blood or adenoidal mononuclear cells were stained with fluorochrome-conjugated monoclonal antibodies, after which the distribution of different cell types was evaluated by analysis with a Facscan flow cytometer (Becton Dickinson, San Jose, Calif). The following fluorochrome-conjugated monoclonal antibodies were used: fluorescein isothiocyanate (FITC)-conjugated anti-CD3 (clone SK7; Becton Dickinson), CyCrome-conjugated anti-CD4 (clone RPA-T4; Pharmingen, San Diego, Calif), and phycoerythrin (PE)-conjugated anti-CD69 (clone TP1.55.3; Coulter, Miami, Fla).

Target Cells and Cytotoxicity Assay. K562 and HL-60 cell lines were used as targets in cytotoxicity assays. The cell lines were purchased from the American Tissue Type Collection (Rockville, Md) and were tested monthly to ensure the absence of *Mycoplasma* infection. Cells were cultured in RPMI 1640 with 10% fetal calf serum (KC Biological, Lexington, Ky). Cytotoxic activity was evaluated by means of a 4-hour sodium chromate 51-release cytotoxicity assay.⁸ The target cells were labeled with 0.1 µCi of sodium chromate 51 for 2 hours and were washed once. Labeled targets (5×10^3 per well) were added to each well of a 96-well U-bottom microtiter plate in 100-µL volume. Effector cells were added in 100-µL vol-

ume to give effector-to-target ratios ranging from 1.5:1 to 50:1. After a 4-hour incubation, 100 µL of supernatant was harvested, and specific cytotoxicity was calculated as follows⁸: %cytotoxicity = [(mean experimental cpm – spontaneous release cpm)/(maximal release cpm – spontaneous release cpm)] × 100.

RESULTS

Expression of CD69 in Adenoidal and Peripheral Blood Mononuclear Cells. One of the earliest cell surface antigens expressed by lymphocytes after activation is CD69, which is detectable within 1 hour of ligation of the T or B cell receptor.⁷ We used flow cytometry to detect the expression of CD69 in lymphocyte subpopulations (Fig 1). The expression of CD69 was analyzed in CD3+ T lymphocytes and in CD3- cells comprising mainly B lymphocytes. Expression of CD69 was then analyzed separately in CD3+, CD4+ helper T lymphocytes and in CD3+, CD4- T lymphocytes, which comprised mainly CD8+ T lymphocytes.

It can be seen in Fig 1 and the Table that the expression of CD69 was more pronounced in adenoidal T and B cells than in peripheral blood cells. The mean percentage of the proportion of CD4+ cells expressing CD69+ to all CD4+ T lymphocytes was 4.6% in peripheral blood and 58.1% in the adenoids ($p < .00001$, Student's *t*-test). The expression of CD69 in adenoidal CD3+, CD4- lymphocytes (suppressor-cytotoxic cells) was also higher (mean, 21.2%) than in peripheral blood CD4- T lymphocytes (mean, 15.1%). However, the difference was not statistically significant.

Induction of CD69 Expression. Peripheral blood mononuclear cells were incubated overnight with glutaraldehyde-fixed bacteria, and the expression of the activation antigen CD69 was measured. Bacterial contact activated peripheral blood T and B lymphocytes to express CD69 (Fig 2A-C, G-I). It could be seen that the effect of *A. otitidis* on CD69 expression was weaker than the effect of *S. aureus* and *S. minnesota*.

We then isolated adenoidal lymphocytes from children who underwent adenoidectomy on the basis of recurrent ear infections and stimulated the cells with the 3 different bacteria (Fig 2). It could be seen that even though the expression of CD69 was already quite high, both *S. aureus* and *S. minnesota* were able to further activate adenoidal T and B cells to a small extent (Fig 2E, F, K, L). The stimulatory effect of *A. otitidis* was weaker (Fig 2D, J).

We then analyzed the expression of CD69 in bacterially activated CD3+, CD4+ helper and CD3+, CD4- suppressor-cytotoxic T cells (Fig 3). Among

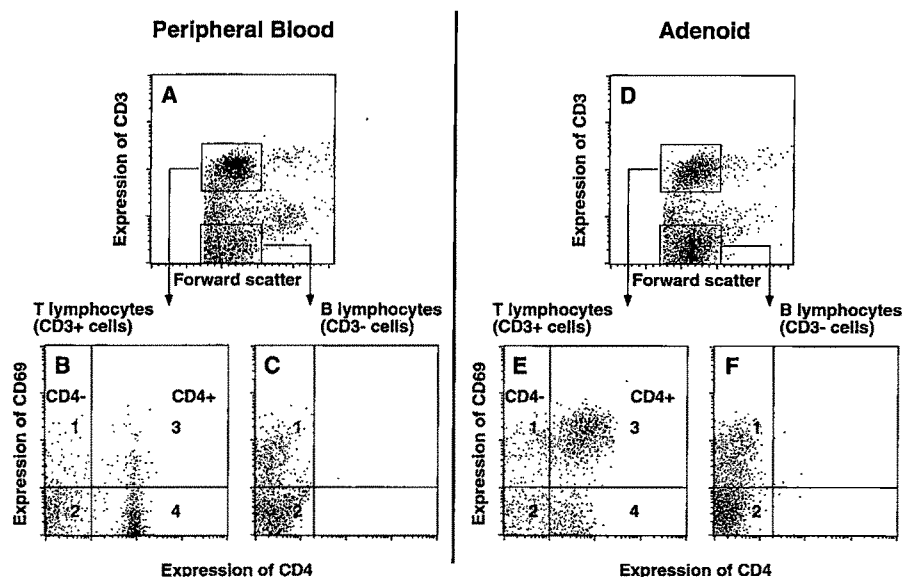


Fig 1. Expression of CD69 in peripheral blood and adenoidal mononuclear cells. Peripheral blood mononuclear (A-C) and adenoidal cells (D-F) were simultaneously stained with fluorescein isothiocyanate (FITC)-conjugated anti-CD3, phycoerythrin (PE)-conjugated anti-CD69, and CyCrome-conjugated anti-CD4 antibodies and were analyzed by flow cytometry. Expression of T lymphocyte antigen receptor antigen CD3 in individual cells was plotted against forward scatter, which is a measure of cell size (A,D). T and B lymphocyte subpopulations were then selected on basis of CD3 expression and forward scatter characteristics for further analysis. Upper boxes in A and D represent CD3+ T lymphocytes, and lower boxes in A and D represent mainly B lymphocytes. More than 95% of selected adenoidal CD3- lymphocytes were B lymphocytes as analyzed by expression of CD19 (data not shown). Selected peripheral blood CD3- population included also monocytes and natural killer cells. Expression of CD69 and CD4 was then analyzed in above selected T (B,E) and B lymphocyte populations (C,F). Percentage of CD69+ cells in peripheral blood CD4+,CD3+ T lymphocytes was calculated by dividing number of cells in quadrant 3 of B by total number of CD4+,CD3+ T lymphocytes (quadrants 3 and 4 of B). More than 90% of CD4-,CD3+ T lymphocytes were CD8+ T lymphocytes (data not shown). Percentage of CD69+ cells in CD8+ T lymphocytes was calculated by dividing number of cells in quadrant 1 of B by total number of CD4-,CD3+ T lymphocytes (quadrants 1 and 2 of B). Percentage of CD69+ cells in peripheral blood B lymphocytes was calculated by dividing number of cells in quadrant 1 of C by total number of B lymphocytes (quadrants 1 and 2 of C). Percentages of CD69+ cells in adenoidal CD4+ and CD8+ T lymphocytes and B lymphocytes were determined as explained for peripheral blood mononuclear cells.

the peripheral blood CD3+ T lymphocytes, the induction of CD69 expression after contact with *A. otitidis* was confined mainly to CD3+,CD4- suppressor-cytotoxic T cells (Fig 3A,G; $p = .0164$, Student's *t*-test). The other bacteria also activated CD3+,CD4+ cells, even though the effect was more pronounced on CD3+,CD4- cells (Fig 3B,C,H,I).

Among the adenoidal cells, it was seen that contact with *A. otitidis* was able to further stimulate adenoidal CD3+, CD4- T lymphocytes (Fig 3J; $p = .0270$, Student's *t*-test). The stimulatory effect of *A. otitidis* on CD3+,CD4+ cells was not significant (Fig 3D). The effect of *S. aureus* and *S. minnesota* on CD69 expression in both CD3+,CD4+ and CD3+,CD4- cells

was stronger than the effect of *A. otitidis* (Fig 3E,F, K,L).

We also tested the effect of a bacterial cell wall component LTA, but it gave a clearly weaker stimulation than *A. otitidis* (data not shown).

Induction of Natural Killer Cell Activity. The observed effect of *A. otitidis* on CD8+ T lymphocytes prompted us to study whether *A. otitidis* would have any effect in another cytotoxic and immunoregulatory system, namely, in the induction of natural killer cell activity. Peripheral blood mononuclear cells were co-incubated with bacteria, and cytolytic activity was assayed against HL-60 and K562 tumor cell lines, which are model cell lines that serve as targets for natural killer cell cytotoxicity. Contact of lymphocytes with *A. otitidis* did induce a small cytotoxic activity, but the magnitude of stimulation was clearly not as potent as that induced by *S. minnesota* or *S. aureus* (Fig 4). Adenoidal tissue contained no significant natural killer cell activity (data not shown).

DISCUSSION

Otitis media with effusion is generally considered to be a direct continuation of the inflammatory pro-

EXPRESSION OF ACTIVATION ANTIGEN CD69 IN PERIPHERAL BLOOD AND ADENOIDAL LYMPHOCYTES

Cells	Peripheral Blood	Adenoid
B (CD3-)	45.3 ± 10.0	32.2 ± 9.7
T (CD3+)	9.6 ± 3.4	52.2 ± 5.1
Helper (CD3+,CD4+)	4.6 ± 2.1	58.1 ± 9.0
Suppressor-cytotoxic (CD3+,CD4-)	15.1 ± 3.9	21.2 ± 8.5

Data are expressed as mean percentage ± SD of 6 experiments.

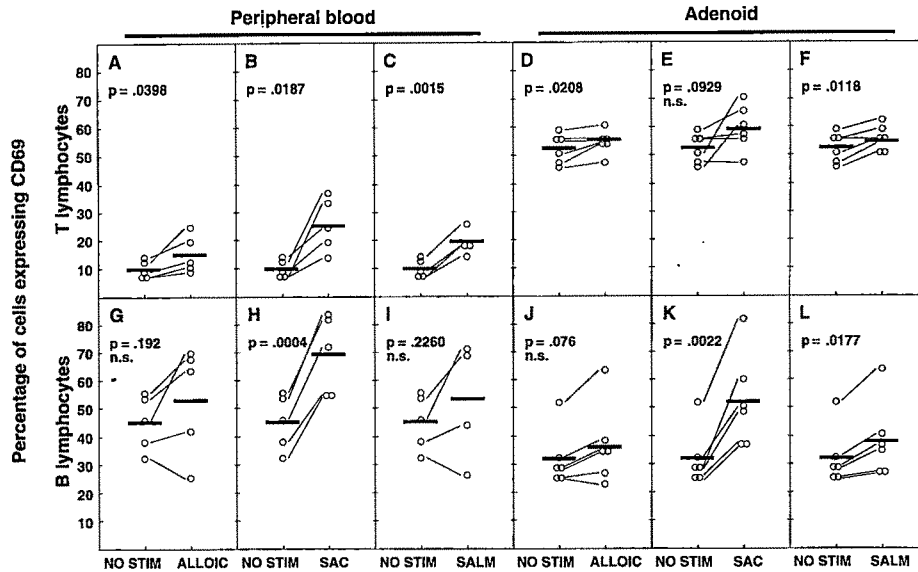


Fig 2. Induction of CD69 expression in T and B lymphocytes by *Alloicoccus otitidis*. Peripheral blood (A-C,G-I) and adenoidal (D-F,J-L) mononuclear cells were incubated overnight with glutaraldehyde-fixed *A otitidis* (ALLOIC), *Staphylococcus aureus* (SAC), and *Salmonella minnesota* (SALM). After incubation, cells were stained with FITC-conjugated anti-CD3 and PE-conjugated anti-CD69 antibodies and were analyzed by flow cytometry. Percentage of CD69+,CD3+ cells of all CD3+ T lymphocytes (A-F) and percentage of CD69+,CD3- cells of all CD3- cells (B lymphocytes; G-L) after treatment with and without bacteria are shown on y-axis. Circles representing values from each individual donor are connected with lines. Thick lines represent mean percentages of each treatment. Statistical significance of difference between no stimulation and stimulation with bacteria is given in each frame, and was calculated with Student's *t*-test for paired samples.

cesses that occur during prolonged or recurrent episodes of acute otitis media. This is evident in light of the findings that nearly all cases of OME have histories of acute otitis media⁹ and by studies with experimental otitis media carried out in animals.¹⁰ These observations suggest that OME has an infectious ori-

gin. However, microbial cultures of middle ear aspirates yield positive results in only a fraction (ranging from 20% to 40%) of all cases of OME. The pathogenic bacteria most often encountered on microbial cultures include *S pneumoniae*, *H influenzae*, and *M catarrhalis*. Recently, PCR techniques have

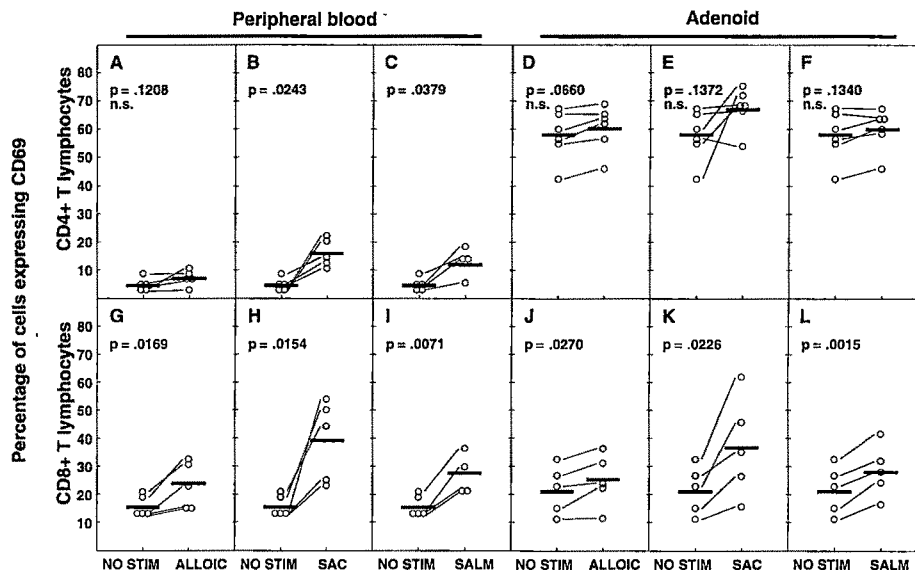


Fig 3. Induction of CD69 expression in CD4+ helper and in CD8+ cytotoxic-suppressor CD3+ T lymphocytes by *A otitidis*. Peripheral blood (A-C,G-I) and adenoidal (D-F,J-L) mononuclear cells were incubated overnight with glutaraldehyde-fixed *A otitidis* (ALLOIC), *S aureus* (SAC), and *S minnesota* (SALM) bacteria. After incubation, cells were stained with FITC-conjugated anti-CD3, PE-conjugated anti-CD69, and CyCrome-conjugated anti-CD4 antibodies and were analyzed by flow cytometry. Percentage of CD69+ cells of all CD4+ T lymphocytes (A-F) and percentage of CD69+ cells of all CD8+ T lymphocytes (G-L) after treatment with and without bacteria are shown on y-axis. Circles representing values from each individual donor are connected with lines. Thick lines represent mean percentages of each treatment. Statistical significance of difference between no stimulation and stimulation with bacteria is given in each frame, and was calculated with Student's *t*-test for paired samples.



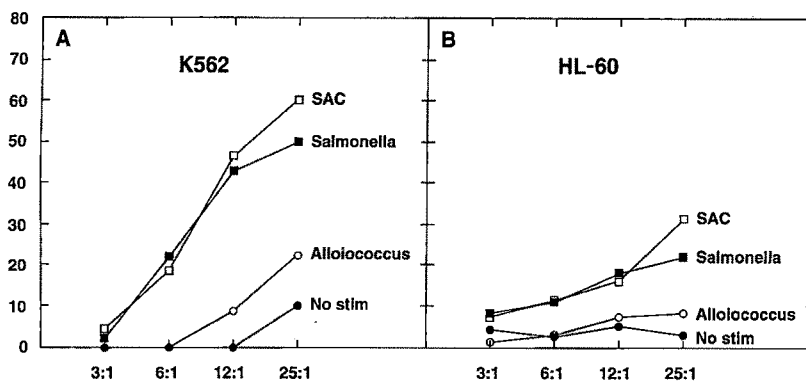


Fig 4. Stimulation of natural killer cell activity by *A. otitidis*. Peripheral blood mononuclear cells were incubated with glutaraldehyde-fixed bacteria overnight (*A. otitidis* [Alloiooccus], *S. aureus* [SAC], and *S. minnesota* [Salmonella]). Cells were subsequently tested for cytotoxic activity against chromium-labeled target cell lines K562 (A) and HL-60 (B) in 4-hour chromium release assay at different effector (stimulated peripheral blood mononuclear cells)-to-target (K562 and HL-60 cell lines) ratios (x-axis). Specific cytotoxicity is shown on y-axis as measured by percentage of chromium released from labeled target cells.

been adapted to measure microbial DNA in the middle ear aspirates. With these methods, the frequency of middle ear aspirate microorganism-positive cases among all cases of OME has increased to as much as 90%.

Alloiooccus otitidis, a gram-positive bacterium, has been cultured from middle ear aspirate. Studies by PCR have revealed that it can be detected in as many as 20% of middle ear aspirates of patients with OME. This finding has raised the possibility that *A. otitidis* may have a pathogenic role in the development of OME. The concept is somewhat disturbed by the fact that *A. otitidis* is found quite infrequently in bacterial cultures of middle ear aspirates.

We developed an in vitro model using peripheral blood and adenoidal lymphocytes to study the interplay between lymphocytes and *A. otitidis*. An in vitro model has previously been used to study the B lymphocyte responses of the human adenoid in terms of antibody production to respiratory antigens.^{11,12} However, these experiments measure antibody synthesis, which is a relatively late response, and require the incubation of the stimulating antigen for several days in vitro. We wanted to study whether *A. otitidis* has immediate effects on lymphocyte activation status. Our results show clearly that *A. otitidis* has immunostimulatory potential, as measured by the induction of expression of CD69 in adenoidal and peripheral blood CD8+ suppressor-cytotoxic T lymphocytes.

The level of expression of CD69 in adenoidal CD8+ suppressor-cytotoxic T lymphocytes induced by *A. otitidis* was comparable with the level of expression of CD69 induced by *S. minnesota* but weaker than the expression of CD69 induced by *S. aureus*. We therefore wanted to analyze whether *A. otitidis* could induce activity in another cytotoxic cell population, namely, whether *A. otitidis* could augment natural killer cell activity. It was found that *A. otitidis* had natural killer cell stimulatory capacity that was less potent than that of *S. aureus* and *S. minnesota*. The results indicate that *A. otitidis* has a unique immunostimulatory capacity that is mainly restricted to

CD8+ suppressor-cytotoxic T lymphocytes.

We then wanted to probe which component of *A. otitidis* was responsible for the immunostimulating activity. Modulation of immune responses can be achieved by both gram-negative and gram-positive bacteria, but via different molecules. Lipopolysaccharide of gram-negative bacteria induces monocyte production of interleukin-12, which in turn is a potent stimulator of interferon- γ production by natural killer cells and T cells. Gram-positive bacteria also induce interleukin-12 production by monocytes, and this effect has been reported to be mediated by LTA.¹³ Therefore, we used the bacterial cell wall component LTA from *S. pyogenes* as a control to stimulate immune cells. However, LTA stimulation yielded clearly weaker responses than whole *A. otitidis* bacteria (data not shown).

The effect of soluble bacterial extracts on lymphocytes may be different from the effect of whole bacteria. In a recent study, whole killed BCG (bacille Calmette-Guérin) bacteria stimulated preferentially α - β CD4+ T cells into proliferation, whereas soluble extracts of the bacteria stimulated preferentially V γ 9+ and V δ 2+ cells.¹⁴ In monocyte-depleted cell cultures also, the natural killer cells were able to respond to bacterial stimulation by proliferation. In our earlier studies, soluble extracts from *Helicobacter pylori* did not induce natural killer cell activity, whereas whole bacteria were quite good inducers.¹⁵ Altogether, it can be concluded that *A. otitidis* may use mechanisms other than LTA to stimulate immune cells. This raises the possibility that *A. otitidis* may have developed a specific machinery to interact with immune cells that may help *A. otitidis* to escape immune surveillance and result in the survival of *A. otitidis* in the middle ear cavity.

When addressing the putative pathogenic role of *A. otitidis*, one must take into account the interplay between immune cells and the challenging microbes. This is especially important in chronic infections such as OME. In chronic infections such as gastritis caused by *H. pylori* or Lyme's disease caused by *Borrelia*

burgdorferi, microbes that have a seemingly low acute pathogenic capability use delicate interactions with immune cells that help them to survive attacks by the immune system, which may provide a selection advantage in microbial evolution.

Adenoids are thought to play an important role in the pathogenesis of OME, as implicated by the beneficial effect of adenoidectomy in the treatment of otitis media. We have previously shown that conversion of naive to memory phenotype T lymphocytes occurs in the adenoids.¹⁶ This differentiation process of lymphocytes in the adenoids may potentially be affected by changes in local microbial flora¹⁷ and by infectious processes involving the adenoids.¹⁸ Persistent viral or bacterial infections may lead to alterations in the function of T and B lymphocytes and antigen-presenting cells. Several studies have suggested that there are differences in the numbers of adenoidal dendritic cells, monocytes-macrophages, and activated lymphocytes in children who have OME as compared with children who have no history of middle ear disease.¹⁸⁻²⁰ Therefore, it is evident that the putative pathogenic role played by *A. otitidis* may involve interactions of *A. otitidis* with immune cells of the adenoids.

It is noteworthy that *A. otitidis* induced the activa-

tion of CD8+ suppressor-cytotoxic T lymphocytes, which have been reported to suppress B lymphocyte responses. This finding raises the possibility that *A. otitidis* may suppress antibody synthesis, resulting in inefficient elimination of *A. otitidis* in the tympanum and in a selective advantage of *A. otitidis*. This possibility is made even more tempting by the observation that antibody-mediated immunity has been reported to be somewhat compromised in children with recurrent otitis media or OME. Levels of serum antibodies to pneumococcus²¹ and nontypeable *H. influenzae*²² and spontaneous adenoidal antibody synthesis in vitro^{23,24} have been reported to be decreased in children with recurrent otitis media or with OME as compared with children who have no history of recurrent middle ear infections.

On the other hand, one may argue that stimulation of CD8+ cells by bacterial contact may be beneficial in the combat against microbes in intracellular locations. Clearly, the pathogenic role of *A. otitidis* in OME cannot be judged by the present experiments. However, contact of *A. otitidis* with adenoidal lymphocytes in vivo is likely to have direct immunostimulatory effects, which may have an effect on the colonization of the adenoids by *A. otitidis* or other bacteria.

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VERTICAL PARTIAL LARYNGECTOMY VERSUS SUPRACRICOID PARTIAL LARYNGECTOMY FOR SELECTED CARCINOMAS OF THE TRUE VOCAL CORD CLASSIFIED AS T2N0

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From an inception cohort of 204 patients with squamous cell carcinoma of the true vocal cord classified as T2N0 and a minimum of 3 years of follow-up, the authors compare the oncological and functional outcomes following vertical partial laryngectomy (group 1; 85 patients) and supracricoid partial laryngectomy (group 2; 119 patients). The 10-year actuarial survival estimate was 46.2% for group 1 and 66.4% for group 2. Survival was statistically more likely to be reduced ($p = .019$) in group 1 than in group 2. The 10-year actuarial local control estimate was 69.3% for group 1 and 94.6% for group 2. Local recurrence was statistically more likely to occur ($p < .0001$) in group 1 than in group 2. Salvage treatment resulted in an overall 94.1% local control rate and a 78.1% laryngeal preservation rate for group 1 and an overall 99.2% local control rate and a 94.9% laryngeal preservation rate for group 2. The 10-year actuarial nodal control estimate was 81.7% for group 1 and 93.7% for group 2. Nodal recurrence was statistically more likely to occur ($p = .028$) in group 1 than in group 2. The 10-year actuarial estimate for patients without distant metastasis was 84.6% for group 1 and 95.1% for group 2. Distant metastasis was statistically more likely to occur ($p = .05$) in group 1 than in group 2. The hospital mortality rate was 1.2% for group 1 and 0.8% for group 2. The incidence of permanent gastrostomy was 0% for group 1 and 2.4% for group 2. The incidence of permanent tracheostomy was 1.2% for group 1 and 0.8% for group 2. The incidence of completion laryngectomy due to functional problems was 1.2% for group 1 and 0.8% for group 2.

KEY WORDS — partial laryngectomy, T2 glottic carcinoma.

INTRODUCTION

In past years, vertical partial laryngectomy and radiotherapy were the conventional conservative treatment methods advocated in patients with squamous cell carcinoma of the true vocal cord classified as T2N0.¹⁻⁹ After the initial description of supracricoid partial laryngectomy with cricothyroidopiglottopexy, initially termed subtotal laryngectomy by Piquet et al,¹⁰ various reports¹¹⁻¹⁷ documented the extremely low incidence of local recurrence when this surgical procedure was performed in patients with squamous cell carcinoma of the true vocal cord classified as T2N0. However, to our knowledge, no report has yet compared the results achieved with supracricoid partial laryngectomy and conventional vertical partial laryngectomy in patients with squamous cell carcinoma of the glottis classified as T2.

At Laënnec Hospital, the supracricoid partial laryngectomy with cricothyroidopiglottopexy procedure, introduced in the early 1970s, progressively took over the conventional vertical partial laryngectomy in patients with invasive squamous cell carcinoma of the true vocal cord classified as T2N0.^{6,11} The present

retrospective study, based upon an inception cohort of 204 patients with a minimum of 3 years of follow-up, was designed to evaluate the long-term consequences of this change in our conservative surgical approach. More specifically, our report intended to compare and analyze the oncological and functional outcomes after vertical partial laryngectomy (group 1; 85 patients) and supracricoid partial laryngectomy with cricothyroidopiglottopexy (group 2; 119 patients). The emphasis was placed on the comparison of rates of survival, local control, nodal control, and distant metastasis control, as well as the incidence of permanent gastrostomy, permanent tracheostomy, and completion total laryngectomy and overall laryngeal preservation rate.

PATIENTS AND METHODS

The present retrospective study was based on the analysis of the medical files, operative charts, and pathological reports of 204 patients with moderately to well-differentiated squamous cell carcinoma of the true vocal cord classified as T2N0, according to the 1997 American Joint Committee on Cancer and Union Internationale Contre le Cancer staging classifica-

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TABLE 1. STATISTICAL COMPARISONS BETWEEN CHARACTERISTICS OF STUDY GROUPS

	Group 1	Group 2	p
Age (y)			
Mean	60	57	.009
Range	44-90	28-85	>.05
Age >65 years	32.9%	25.2%	.29
Gender			.08
Male	98.8%	92.6%	
Female	1.2%	7.4%	
Tobacco intake (pack-years)			.31
Mean	35	40	
Range	0-238	0-100	
Alcohol intake (g/L per day)			
0	24.1%	10.2%	.01
1-40	31.3%	34.7%	.72
41-80	32.5%	33.1%	.94
>81	12%	22%	.10
Significant medical history	48.2%	39.5%	.27

Percentage data are percentage of each population.
Group 1 — 85 patients who underwent vertical partial laryngectomy;
group 2 — 119 patients who underwent supracricoid partial laryngectomy with cricohyoidoepiglottopexy.

tion systems,^{18,19} who were consecutively managed at Laënnec Hospital during the years 1962 to 1995 with a partial laryngectomy via an open surgical approach.

Patients with squamous cell carcinoma of the true vocal cord classified as T2N0 who had been managed previously with radiotherapy or endoscopic carbon dioxide laser excision, and patients with tumors transglottic, subglottic, or supraglottic in origin, with tumors originating from the anterior commissure, with a simultaneous second primary tumor, and with tumors not amenable to partial laryngectomy for oncological and/or functional reasons were excluded from the present study.

Group 1 consisted of 85 patients managed with vertical partial laryngectomy. Group 2 consisted of 119 patients managed with supracricoid partial laryngectomy with cricohyoidoepiglottopexy.¹¹ Statistical analysis, using the parametric χ^2 test for qualitative variables and the nonparametric Mann-Whitney U test for quantitative variables (significance being set at the .05 level), did not demonstrate any significant differences between group 1 and group 2 in terms of gender, tobacco intake, alcohol intake, percentage of patients with a significant medical history, or percentage of patients older than 65 years of age (Table 1). However, the mean age of patients was 3 years older in group 1 than in group 2 (Table 1). Also, no significant statistical difference could be demonstrated in terms of comorbidity between the 2 groups of patients by use of the Charlson et al²⁰ comorbidity

TABLE 2. STATISTICAL COMPARISONS OF TUMOR PARAMETERS BETWEEN STUDY GROUPS

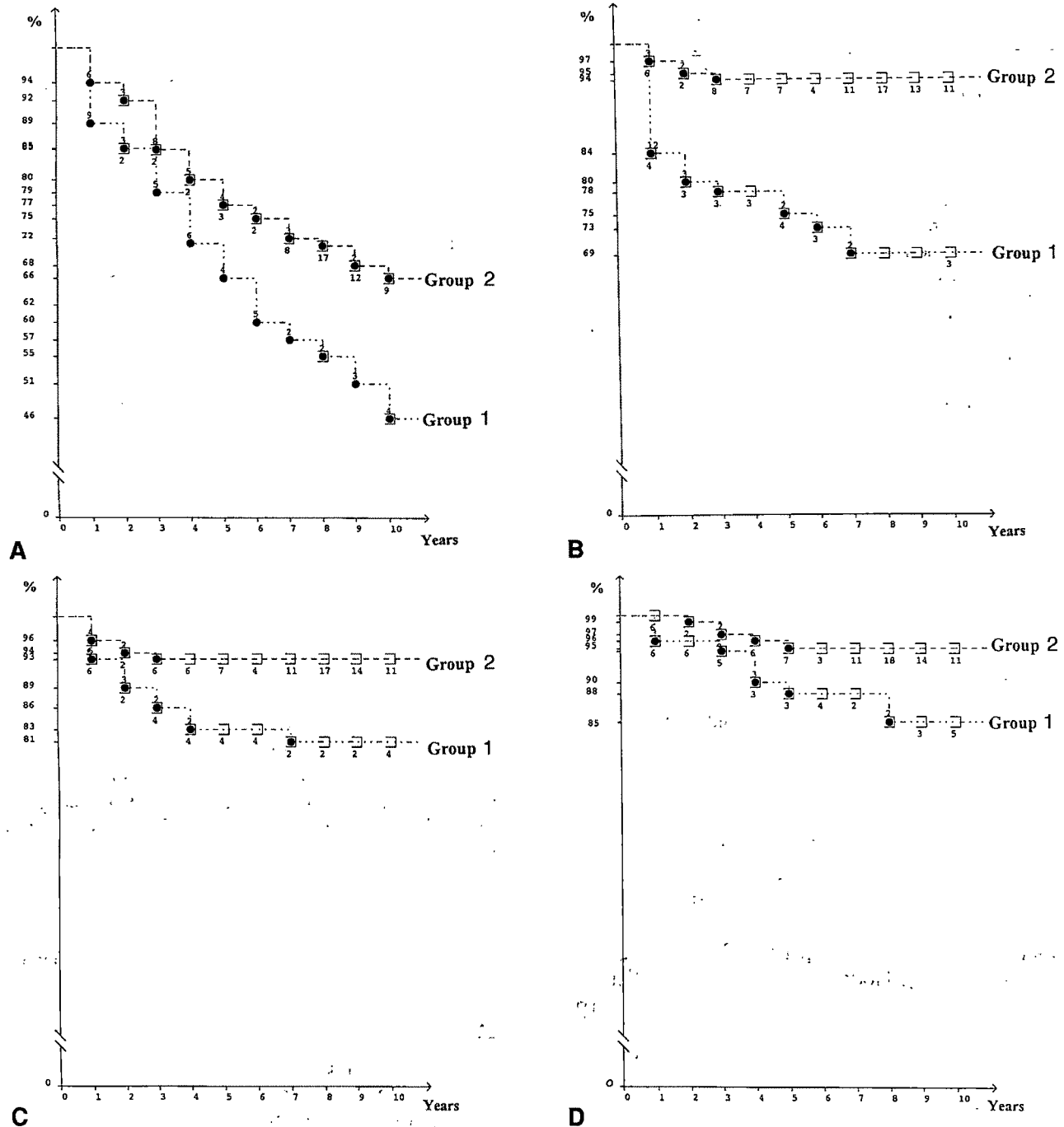
Specific Tumor Features	Group 1 (%)	Group 2 (%)	p
Tumor location			
Anterior commissure	40	50.4	.18
Contralateral true vocal cord	23.5	33.9	.14
Floor of ventricle	62.4	77.7	.025
False vocal cord	10.6	14.9	.49
Lateral subglottis	30.6	12.4	.002
Anterior subglottis	14.1	16.5	.78
Petiole of epiglottis	7.1	7.4	.86
Anterior aspect of arytenoid	14.1	18.2	.55
Impaired motion of true vocal cord	35.3	44.6	.23
Impaired motion of arytenoid	5.9	8.3	.70
Chronic laryngitis	27.1	35.8	.24

Data are presented as percentage of each population.

index-weighted score (χ^2 test, $p = .62$). As depicted in Table 2, the only significant differences between group 1 and group 2 in terms of specific tumor features were 1) the subglottic extent of tumor more frequently noted in group 1 patients than in group 2 patients, and 2) the invasion of the floor of the ventricle more frequently noted in group 2 patients than in group 1 patients. Pathological analysis of the specimens did not demonstrate any significant statistical difference in terms of degree of differentiation of the tumor or in margins of resection. The percentage of patients with positive margins varied from 8.2% in group 1 (7/85) to 3.4% in group 2 (4/119). Postoperative radiotherapy to the larynx was not used in the present study; rather, patients with positive margins were managed expectantly with a "watch and wait" policy.

Of the 204 patients in our series, 118 underwent an induction chemotherapy regimen before the partial laryngectomy. The percentage of patients managed with induction chemotherapy varied significantly ($p = .0001$), from 18.8% in group 1 (16/85) to 85.7% in group 2 (102/119).

Follow-up data were collected via periodic visits to our clinic. All patients but 2 in group 1 (2.4%) and 1 in group 2 (0.8%) were followed for a minimum of 3 years or until death. Statistical analysis of rates of survival, local control, nodal control, and control of distant metastasis was based on the product limit method of Kaplan and Meier.²¹ The log rank test was used for statistical comparison between the 2 groups. The parametric χ^2 test, Wolf G test, and Fisher test were used for statistical analysis of the relationships between survival, local recurrence, nodal recurrence, and distant metastasis. Statistical significance was set at the .05 level.



Kaplan-Meier²¹ analyses. A) Survival. Circles — patients dead of initial disease; brackets — patients lost to follow-up. B) Local control. Circles — patients dead of initial disease; brackets — patients lost to follow-up. C) Nodal control. Circles — patients with nodal failure; brackets — patients dead or lost to follow-up. D) Control of distant metastasis. Circles — patients with distant metastasis; brackets — patients dead or lost to follow-up.

RESULTS

Survival Rate. The 10-year actuarial survival estimate was 46.2% for group 1 patients and 66.4% for group 2 patients (see Figure, A).²¹ Survival was statistically more likely to be reduced in group 1 than in group 2 ($p = .019$). According to the log rank test, the risk of death was 1.5 times higher in group 1 than in group 2 (see Figure, A). Analysis of the causes of death noted that 1.2% of patients (1/85) in group

1 and 1.7% of patients (2/119) in group 2 died of a surgery-related complication, whereas 21.2% of patients (18/85) in group 1 and 8.4% of patients (10/119) in group 2 died of locoregional recurrence and/or distant metastasis. The use of induction chemotherapy never resulted in death. Overall, death was statistically more likely to occur if patients developed a local recurrence ($p < .0001$), a nodal recurrence ($p < .0001$), or a distant metastasis ($p < .0001$).

TABLE 3. COMPLICATIONS AFTER PARTIAL LARYNGEAL SURGERY

Complications	Group 1 (%)	Group 2 (%)
Medical complications		
Lower limb arterial ischemia	0	0.8
Severe respiratory insufficiency	1.2	0.8
Cardiac decompensation	2.4	1.6
Pneumonia from aspiration	1.2	10.7
Surgical complications		
Postoperative hematoma	2.4	2.4
Cervical skin necrosis	0	0.8
Laryngeal chondritis	1.2	0
Ruptured pexy	0	1.6
Laryngotracheal stenosis	1.2	1.6
Laryngocele	3.6	4.8

Data are presented as percentage of each population.

Local Control. Overall, a local recurrence developed in 33 patients. The 10-year actuarial local control estimate was 69.3% for group 1 and 94.6% for group 2 (see Figure, B). Local control was statistically more likely to be reduced in group 1 than in group 2 ($p < .0001$). According to the log rank test, the risk of a local recurrence's developing was 5.8 times higher in group 1 than in group 2 (see Figure, B). Salvage treatment resulted in an overall 94.1% local control rate in group 1 and a 99.2% local control rate in group 2, together with a 78.1% laryngeal preservation rate in group 1 and a 94.9% laryngeal preservation rate in group 2.

Nodal Control. Overall, 25 patients had a nodal recurrence. Nodal recurrence was statistically more likely to occur in patients who had a local recurrence ($p < .0001$). The 10-year actuarial nodal control estimate was 81.7% for group 1 and 93.7% for group 2 (see Figure, C). Nodal recurrence was statistically more likely to occur in group 1 than in group 2 ($p = .028$). According to the log rank test, the risk of a nodal recurrence's developing was 2.8 times higher in group 1 than in group 2. In patients with nodal recurrence, the management of the neck consisted of neck dissection together with postoperative radiotherapy.

Control of Distant Metastasis. Overall, 15 patients developed a distant metastasis. Distant metastasis was statistically more likely to occur in patients who had a local recurrence ($p = .0003$) or a nodal recurrence ($p = .0001$). The 10-year actuarial estimate for patients without a distant metastasis was 84.6% for group 1 and 95.1% for group 2 (see Figure, D). A distant metastasis was statistically more likely to occur in group 1 than in group 2 ($p = .05$). According to the log rank test, the risk of a distant metastasis's developing was 3 times higher in group 1 than in

group 2 (see Figure, D).

Functional Outcome. The types and incidences of severe postoperative complications in both groups are presented in Table 3. The hospital mortality rate was 1.2% in group 1 (1/85) and 0.8% (1/119) in group 2. Pneumonia from aspiration was the only complication of which the incidence was significantly higher in group 2 than in group 1 (Table 3). Pneumonia from aspiration led to death in 1 patient in group 2. The incidence of permanent gastrostomy was 0% in group 1 and 2.5% (3/119) in group 2. The incidence of permanent tracheostomy was 1.2% (1/85) in group 1 and 2.5% (3/119) in group 2. The incidence of completion laryngectomy due to functional problems was 1.2% (1/85) in group 1 and 0.8% (1/119) in group 2.

DISCUSSION

Various reports have documented the oncological and functional results achieved with radiotherapy or vertical partial laryngectomy alone for selected squamous cell carcinoma of the true vocal cord classified as T2.¹⁻⁹ However, in series with more than 100 patients with selected squamous cell carcinoma of the glottis classified as T2, the local recurrence rate after vertical partial laryngectomy or radiotherapy alone is far from being negligible and has been reported to vary from 17% to 40%.¹⁻⁹ Piquet et al,¹⁰ in 1974, described a new surgical approach, now termed supracricoid partial laryngectomy with cricohyoidoepiglottopexy, for the management of selected glottic carcinomas that would usually be treated with a vertical partial laryngectomy. In a large number of series, supracricoid partial laryngectomy with cricohyoidoepiglottopexy appeared to be a highly valuable option in the face of carcinoma of the true vocal cord classified as T2 amenable to a vertical partial laryngectomy.¹¹⁻¹⁷ However, to our knowledge, no report has yet documented and compared the long-term oncological and functional results achieved by performing supracricoid partial laryngectomy with cricohyoidoepiglottopexy in lieu of vertical partial laryngectomy in patients with an invasive squamous cell carcinoma of the true vocal cord classified as T2N0.

In the present retrospective series based on 204 patients with an invasive squamous cell carcinoma of the true vocal cord classified as T2N0 and a minimum of 3 years of follow-up, 85 patients were treated with a vertical partial laryngectomy (group 1), and 119 patients were treated with a supracricoid partial laryngectomy with cricohyoidoepiglottopexy (group 2). The Kaplan-Meier²¹ analysis revealed that survival was statistically more likely to be reduced in group 1 patients than in group 2 patients ($p = .019$), with a 46.2% 10-year actuarial survival estimate for

group 1 patients and a 66.4% 10-year actuarial survival estimate for group 2 patients (see Figure, A). Although the mean age of patients in group 1 was 3 years younger than the mean age of patients in group 2, the comparison between both groups did not demonstrate any significant statistical difference in terms of gender, tobacco intake, alcohol intake, incidence of significant medical history, percentage of patients older than 65 years of age (Table 1), or comorbidity (according to the Charlson et al²⁰ comorbidity index weighted score). It appears, therefore, that the explanation for the reduced survival rate in group 1 when compared with that of group 2 did not rely on a difference between the populations. Rather, the analysis of the oncological outcome in both groups provided a clue to the significant difference in terms of survival documented in the present study. Analysis of the causes of death revealed that the modification in the surgical approach did not increase the mortality rate, as only 1.2% of patients in group 1 and 1.6% of patients in group 2 died of a surgery-related complication, whereas the hospital mortality rate was 1.2% for group 1 and 0.8% for group 2. Interestingly, the use of induction chemotherapy before partial laryngectomy did not result in an increase in the mortality rate, as death in our series was never related to the completion of induction chemotherapy. On the other hand, 21.2% of patients in group 1 died of locoregional recurrence and/or distant metastasis, versus 8.3% of patients in group 2. Further, as depicted in the Figure, C, nodal recurrence was statistically more likely to occur in group 1 than in group 2 ($p = .025$), with an 81.7% 10-year actuarial nodal control estimate for group 1 and a 93.7% 10-year actuarial nodal control estimate for group 2 (see Figure, C). Also, distant metastasis was statistically more likely to occur in group 1 than in group 2 ($p = .05$), with an 84.6% 10-year actuarial estimate for patients without a distant metastasis in group 1 and a 95.1% 10-year actuarial estimate for patients without a distant metastasis in group 2 (see Figure, D). The overall analysis of the relationships between survival rate, local recurrence, nodal recurrence, and distant metastasis also documented the importance of local control; strong statistical relationships were noted among local recurrence, nodal recurrence, distant metastasis, and death. In our series, local recurrence resulted in a cascade of oncological events with the consequence of a significant impairment in terms of survival rate.

The evolution toward the use of supracricoid partial laryngectomy with cricothyoidoepiglottopexy in lieu of vertical partial laryngectomy in patients with an invasive squamous cell carcinoma of the true vocal cord classified as T2N0 appears to be highly valuable if the results achieved in the present report are

analyzed in terms of local control. The 10-year actuarial local control estimate was 69.3% for group 1 and 94.6% for group 2 (see Figure, B). Local control was statistically more likely to be reduced in group 1 than in group 2 ($p < .0001$; see Figure, B). A higher incidence of subglottic extent of tumor was noted in group 1 patients (Table 2). However, 1) all the other specific tumor sites were more frequently involved in group 2 than in group 1 (Table 2); 2) the percentage of patients with chronic laryngitis or an impaired motion of the true vocal cord was higher in group 2 than in group 1 (Table 2); 3) the percentage of patients with positive margins of resection after partial laryngectomy did not vary significantly between the groups; and 4) the degree of differentiation of the tumors did not vary significantly between the groups. Such data suggest that the aggressiveness of the tumors was similar among both groups and that no specific tumoral features could explain the reduced local control rates in group 1 patients. Rather, in our opinion, the explanation for the reduced local control rate achieved in group 1 patients relied upon the wider exposure and the wider mucosal and paraglottic space resection performed by using supracricoid partial laryngectomy with cricothyoidoepiglottopexy in lieu of vertical partial laryngectomy. Such an explanation contradicts the dogma that millimeter margins of resection are sufficient when performing oncological resection of endolaryngeal tumors, and suggests that the achievement of wide resection margins in endolaryngeal tumors, as advocated for hypopharyngeal, oropharyngeal, and oral cavity invasive squamous cell carcinoma, might result in a better outcome in terms of local control.

The increase in terms of initial local control in using supracricoid partial laryngectomy with cricothyoidoepiglottopexy noted in our series not only allowed for a better survival rate, but also resulted in an increase in terms of laryngeal preservation. An overall 94.1% local control rate for group 1 and a 99.2% local control rate for group 2, together with a 78.1% laryngeal preservation rate for group 1 and a 94.9% laryngeal preservation rate for group 2, was achieved after salvage treatment. Interesting, also, as depicted in Table 3, is the fact that the use of supracricoid partial laryngectomy with cricothyoidoepiglottopexy in lieu of vertical partial laryngectomy did not result in a significant increase in terms of surgery-related complications, permanent tracheostomy, or completion total laryngectomy for functional reasons. However, the risk of developing pneumonia from aspiration was higher after supracricoid partial laryngectomy with cricothyoidoepiglottopexy than after vertical partial laryngectomy. In most cases, aspiration-related problems were successfully man-

aged expectantly with chest therapy, speech therapy, and antibiotic treatment, as the incidences of permanent gastrostomy and completion total laryngectomy after supracricoid partial laryngectomy with cricohyoidoepiglottopexy were 2.4%, and 0.8%, respectively.

An important and controversial point in the present report is the use of an induction chemotherapy regimen before the completion of partial laryngectomy. A statistical analysis of the role of induction chemotherapy could not be performed, as this presurgical treatment method was significantly more frequently used in group 2 patients than in group 1 patients ($p = .0001$). However, in the reported series^{12-14,16} documenting the use of supracricoid partial laryngectomy with cricohyoidoepiglottopexy without induction chemotherapy in patients with glottic carcinoma classified as T2, the reported local control rates are similar to the one noted in the present report. Therefore, in our series, induction chemotherapy should not be considered as the main factor explaining the better oncological results achieved within group 2 as compared to group 1. One might even wonder whether the use of induction chemotherapy for glottic tumors classified as T2N0 should not be considered as over-treatment. At the present time, no multi-institutional randomized prospective study has been reported documenting a role for induction chemotherapy in patients with early-stage laryngeal cancer. Wolf and Ki Hong²² postulated that there was no role for induction chemotherapy in patients with early-stage laryngeal cancer. However, data suggesting that induction chemotherapy might play a role in the management of early-stage laryngeal cancer have been reported. In the Veterans Affairs Laryngeal Cancer Study Group trial, the review of the characteristics of the 332 patients who were managed with a platinum-based induction chemotherapy regimen noted that 31 patients presented with laryngeal tumors classified as T1 or T2.²³ The cancer in such cases was considered advanced because of the presence of a palpable lymph node, but the tumor within the larynx was, in fact, at an early laryngeal stage. Similarly, Demard et al,²⁴ in a retrospective analysis of the response to platinum-based induction chemotherapy as a justification for modification of the therapeutic strategy for pharyngolaryngeal carcinoma based upon 81 patients, included 25 patients with early-stage laryngeal tumors classified as T1-2. In 1999, Laccourreye et al¹⁷ reported their experience of the use of platinum-based induction chemotherapy regimens in patients with

carcinoma of the glottic larynx classified as T2. This nonrandomized retrospective review of 100 patients and a minimum of 3 years of follow-up noted an 82% clinical response rate. Further, the use of partial laryngeal surgery after platinum-based induction chemotherapy in all patients resulted in an 85.8% 5-year actuarial survival estimate together with a 95.4% 5-year actuarial local control estimate.¹⁷ Of utmost interest was the high incidence of complete histologic regression, noted in 31% of the patients, and the strong significant statistical relationship noted between the achievement of a complete clinical response and a complete histologic regression.¹⁷ A report from our department also suggested that patients with glottic carcinoma classified as T1-3N0 who achieved a complete clinical response could benefit from a treatment with exclusive chemotherapy.²⁵ Such data suggest, in our opinion, that the use of induction chemotherapy in glottic carcinoma classified as T2 is not detrimental. In our opinion, the response to induction chemotherapy should be used to tailor the definitive treatment performed. Schematically, a complete clinical responder should be viewed as an extremely good candidate for either radiotherapy or exclusive chemotherapy, and a nonresponder should be managed with the most aggressive partial laryngectomy available, namely, a supracricoid partial laryngectomy. In partial responders, a discussion based upon the initial tumor location, the initial laryngeal mobility, the degree of response, and the patient's functional status and wishes should be carried out to define the best approach (radiotherapy or partial laryngectomy), as well as the best way to resect the tumor (endoscopic laser; conventional partial laryngectomy, supracricoid partial laryngectomy) when a partial laryngectomy is required.

In conclusion, we are well aware that no absolute and definitive statements can be drawn from the present report, because of the retrospective and historical aspects of this study, as well as the heterogeneity in using induction chemotherapy before partial laryngectomy. However, 1) the homogeneity of the two populations under analysis in terms of tumors, patients, and comorbidity, 2) the very low number of patients lost to follow-up (3%), and 3) the minimum of 3 years of follow-up, together with the data presented, document clearly the value of supracricoid partial laryngectomy with cricohyoidoepiglottopexy and suggest a possible role for a multimodal strategy in patients with tumors of the true vocal cord classified as T2N0.

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RECURRENT LARYNGEAL NERVE TRANSPOSITION IN GUINEA PIGS

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Improved control of prosthetic voice aids for laryngectomees might be possible to obtain with residual laryngeal motor nerve signals. We were able to recover motor signals from the recurrent laryngeal nerve (RLN) by transposing it into the ipsilateral denervated sternohyoid muscle (SH) in 8 guinea pigs. Reinnervation was monitored by electromyographic recordings from surface and intramuscular needle electrodes in awake animals. Within 4 to 14 weeks after surgery, all animals demonstrated laryngeal-like motor activity in the reinnervated SH, including activity during respiration, sniffing, swallowing, and/or vocalizing. After 3 to 6 months, the animals were reanesthetized, and nerve stimulation and section experiments confirmed the RLN as the source of reinnervation in all cases. In several animals, activity of the RLN-innervated SH was demonstrated to be correlated with that of contralateral laryngeal muscles. Histochemical analysis of the SH indicated a unilateral transformation from mostly fatigable to mostly fatigue-resistant fiber types ipsilateral to the RLN transposition, a phenotype more typical of laryngeal muscles. Thus, RLN transposition at the time of laryngectomy may be a method for salvaging laryngeal control signals that could be used to control prosthetic voice devices.

KEY WORDS — alaryngeal speech, artificial larynx, laryngectomy, larynx, prosthesis, recurrent laryngeal nerve.

INTRODUCTION

A majority of individuals who have lost laryngeal function are initially prescribed a handheld vibrator or “electrolarynx” (EL) to generate an artificial voice for alaryngeal speech. Many of these patients adopt the EL as their primary means of alaryngeal speech production, either as a matter of preference or because they are unable to acquire serviceable voice by other means. For example, in a prospective study of 166 laryngectomy patients in the Veterans Administration system, 55% of the surviving group were using an EL 2 years after the laryngectomy.¹ Despite EL prevalence, currently available EL devices produce voice that is reduced in intelligibility and sounds unnatural, thereby drawing unwanted attention to the user.^{2,3} Although EL devices have push-button controls for on-off switching and, in some cases, pitch control, users are not able to modulate pitch, intensity, or onset and offset in a way that approximates the rapid and finely timed manipulation of these parameters in normal speech. In addition, current handheld (controlled) devices preclude speaking while performing tasks that require the use of both hands. Better, hands-free control over these parameters might be possible if laryngeal motor commands could be

obtained and applied to prosthetic control.

At laryngectomy, the motor nerves to the larynx are severed, but there is evidence that they are capable of regeneration. Herrmann⁴ provided a brief account of recurrent laryngeal nerve (RLN) transposition to the sternocleidomastoid muscle (SCM) in 7 patients at the time of laryngectomy. Within 3 months of surgery, electromyography (EMG) activity recorded with needle electrodes from the SCM coincided with respiration and/or attempted phonation in these individuals — a finding that suggested successful RLN transposition to the host SCM. Furthermore, animal studies have demonstrated the natural propensity for cut laryngeal nerves to reinnervate muscle even when steps are taken to prevent regeneration, such as segment removal and ligation.⁵ If a laryngeal nerve is still capable of conveying voice-related action potentials, these signals could, in principle, be used to help control voice prostheses such as the EL. Detecting residual laryngeal neural signals would be greatly facilitated if the laryngeal nerves were allowed to reinnervate a host muscle that would serve as a natural amplifier of the voice-related potentials. These signals could potentially be detected noninvasively from the neck surface above the host muscle

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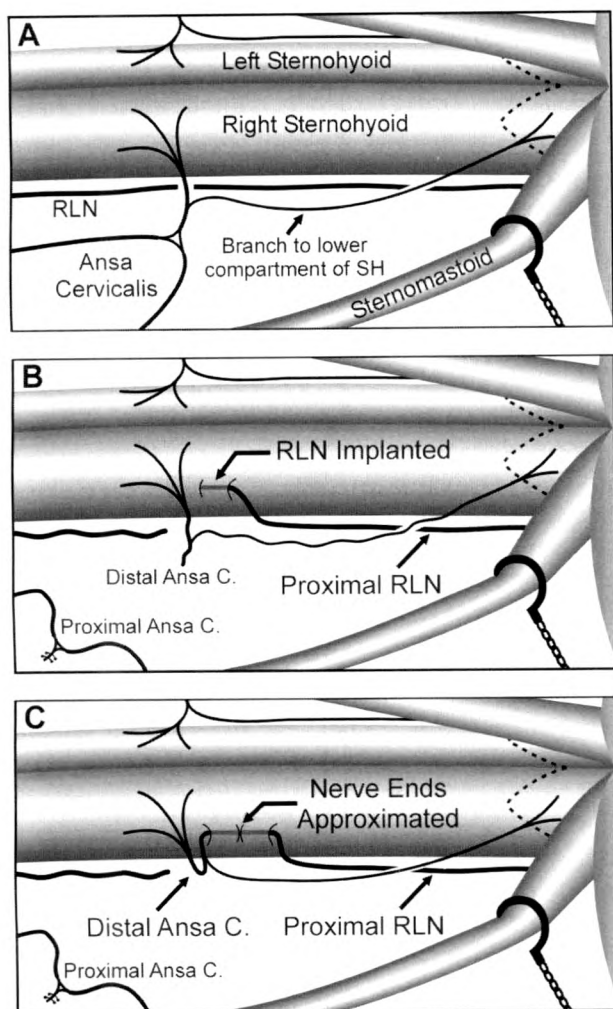


Fig 1. Schematic diagram of unilateral recurrent laryngeal nerve (RLN) transposition methods. A) Normal innervation of sternohyoid muscles (SHs) by ansa cervicalis. B) Cut right proximal RLN was embedded into right SH near point of previous main innervation by ansa cervicalis in 4 animals. C) Cut ends of right proximal RLN and right distal ansa cervicalis were embedded into SH and adjoined to form sutureless neurorrhaphy in 4 animals.

by means of EMG and could be used to control voice prosthetic devices.

To test the feasibility of laryngeal nerve transposition, we performed unilateral RLN transposition in 8 guinea pigs by sectioning the right RLN and directing it to the ipsilateral denervated sternohyoid muscle (SH). Starting 4 weeks after surgery, we periodically compared EMG signals recorded from the neck surface above the RLN-implanted and normal SHs in awake animals while they vocalized and breathed under a variety of conditions. After survival periods of 3 to 6 months, we conducted terminal EMG recording experiments to compare EMG activity in the RLN-innervated SH, in the contralateral SH, and in intrinsic laryngeal muscles during respiration, laryngeal mucosal stimulation, and direct nerve stimu-

lation. To our knowledge, this effort reflects the first attempt to develop a noninvasive method for acquiring neuromotor signals after nerve transposition for prosthetic control.

METHODS

Subjects. Twelve guinea pigs were used in these experiments. In 8 animals, the right RLN was transposed to the right SH, and 4 animals served as unoperated controls. The left SH in each experimental animal also served as a control, in that its innervation was left intact. Animals weighed between 165 and 352 g at the time of nerve transposition, and between 660 and 1,123 g 3 to 6 months later, at the time of painless sacrifice. All procedures were conducted under the auspices of protocols approved by the Massachusetts Eye and Ear Infirmary Animal Care and Use Committee.

Nerve Transposition. Nerve transposition was performed under anesthesia produced with intramuscular ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (5 mg/kg). The right ansa cervicalis (normally supplying the SH) and right RLN were identified and transected. Standard end-to-end nerve connection (neurorrhaphy) with epineurial sutures was not possible because of the small size of the RLN and ansa cervicalis in young guinea pigs. In 4 guinea pigs, approximately 5 mm of the proximal RLN was embedded in the ipsilateral denervated SH, near the penetration of the main ansa cervicalis branch. This was done by tying the cut nerve to 10-0 nylon and pulling the nerve through the muscle with a suture needle. The nerve end was then trimmed and pulled back into the muscle so that the cut end was embedded. In the remaining 4 guinea pigs, the proximal RLN and the distal stump of the ansa cervicalis were pulled into the SH from opposite directions, such that their cut ends were approximated and embedded in the muscle (see Fig 1 legend).

EMG Recording From Awake Animals. The EMG, vocal, and respiratory signals were acquired with Axon Instruments (Foster City, Calif) hardware and software in conjunction with a personal computer. The signals were amplified by a gain of 2,000 to 20,000, bandpass-filtered at 10 to 4,000 Hz, and digitized at 20,000 samples per second. The EMG recordings of SH activity in awake animals were performed by using a custom-made electrode array placed on the skin surface above the SHs, or by using hooked-wire or monopolar needle electrodes (Nicolet Biomedical; 019-772800 and 019-403600, respectively). The skin surface electrode array was a rubber collar, measuring 2.5×19 cm, with Velcro ends. It had 4 blunt steel pins (1.5 mm diameter) spaced 12 mm apart in concave plastic grommets filled with conductive

paste. One pair of electrodes was located above the right SH, and the other pair was above the left SH. A ground was provided by 2 additional blunt pins located 12 mm lateral to the midline pairs.

The EMG recordings were made from the neck surface at multiple intervals ranging from 4 to 20 weeks after nerve transposition. Hooked-wire or monopolar needle recordings were conducted on 5 of the 8 animals, 19 to 25 weeks after surgery. The EMG and microphone signals were obtained during activities associated with intrinsic laryngeal muscle responses, including airway occlusion, sniffing a weak acetic acid solution on a cotton swab, vocalizing, and breathing at rest.

Terminal EMG Recording Procedure. A preanesthetic dose of atropine sulfate (0.06 mg/kg intraperitoneally) was administered, and each animal was deeply anesthetized with an intramuscular injection of droperidol (3 mg/kg)–fentanyl citrate (3 mg/kg) and an intraperitoneal injection of urethane (4.5 mg/kg). Urethane injections of one-quarter the original dose were repeated every 2 to 3 hours until the recordings were complete. Each animal was then given an overdose of pentobarbital sodium (100 mg/kg intraperitoneally) and perfused transcardially with 400 mL of saline followed by 500 mL of 10% neutral buffered formalin.

Enameled nickel-chrome wire (Tophet C, Wilbur B. Driver Co) with 0.5-mm exposed tips or concentric needle electrodes (Nicolet Biomedical, 019-761300) were used to differentially record the EMG activity from the SH and internal laryngeal muscles. Respiratory phases were monitored with a pressure sensor and amplifier (TBM 4; World Precision Instruments, Inc) connected to a water-filled rubber tube (Tygon R-3606) wrapped around the guinea pig's abdomen.

The vagus, RLN, and intact ansa cervicalis were dissected free from surrounding tissues and electrically isolated by submersion in mineral oil. The nerves were then stimulated with 0.3-ms square-wave pulses ranging in amplitude from 0.05 to 4 mA by means of a bipolar electrode-consisting of 2 blunt silver hooks spaced 2 mm apart. The EMG activity was recorded from the right and left SHs in all animals during nerve stimulation, normal breathing, airway occlusion, and mechanical stimulation of the glottal mucosa. In addition, EMG recordings were also made from the intrinsic laryngeal muscles (thyroarytenoid, cricothyroid, and/or posterior cricoarytenoid) in 6 animals during these manipulations. One animal died prematurely during the terminal EMG recording session before nerve stimulation was completed, so data for compound muscle action potentials (CMAPs) were

obtained for 7 of the 8 nerve-transposed animals.

Data analysis for the terminal EMG recordings was performed with custom software written in Matlab. This program measured multiple parameters of the CMAP peaks generated by nerve stimulation, including their amplitude, number, and latency.

Muscle Histochemistry. In 4 animals, the upper thirds of the right and left SH muscles were processed histochemically. Samples were mounted in Tissue-Tek (Miles Inc), frozen rapidly in isopentane, cut transversely on a cryostat into 8- to 12- μ m sections, and mounted on glass slides. Sections were collected in sets for processing with 4 different histochemical procedures. Section sets were stained for myofibrillar adenosinetriphosphatase (ATPase) after acid or alkaline preincubations (4.3, 4.6, and 10.4 pH)⁶ or for succinate dehydrogenase (SDH),⁷ a marker of oxidative metabolic potential.

One representative ATPase-stained section (pH 4.6) from each animal was digitized with a CCD camera connected to a personal computer. All muscle fibers from the representative section were counted and identified as either type 1 or type 2. The distinction between type 1 and type 2 fibers was unequivocal. A randomly selected sample of 100 of the type 2 fibers was further subdivided into fatigable (type 2b) and fatigue-resistant types (2a or 2x) in reference to both the ATPase and SDH reaction product densities.⁸

RESULTS

All 8 animals showed evidence of RLN innervation of the SH based on spontaneous and evoked EMG potentials. In addition, histochemical staining of host SH fibers for ATPase and SDH in 4 animals revealed changes in fiber type populations relative to the intact contralateral side that were consistent with RLN reinnervation.

Vocal-Related EMG Potentials From RLN-Innervated SH. The EMG potentials correlated with phonation were recorded from the neck surface in 5 of the 8 guinea pigs tested. These EMG bursts could be recorded from the right neck surface above the RLN-innervated SH, but were either not evident or relatively weak over the left (control) side of the neck (Fig 2). When present, these weak vocal-related potentials detected from the left neck surface appeared to reflect current spread of potentials emanating from the right neck. The EMG recordings made with monopolar needle and hooked-wire electrodes provided greater selectivity and better signal-to-noise ratios (Fig 2) than skin surface recordings. Vocal-related activity was recorded in all 5 animals tested with

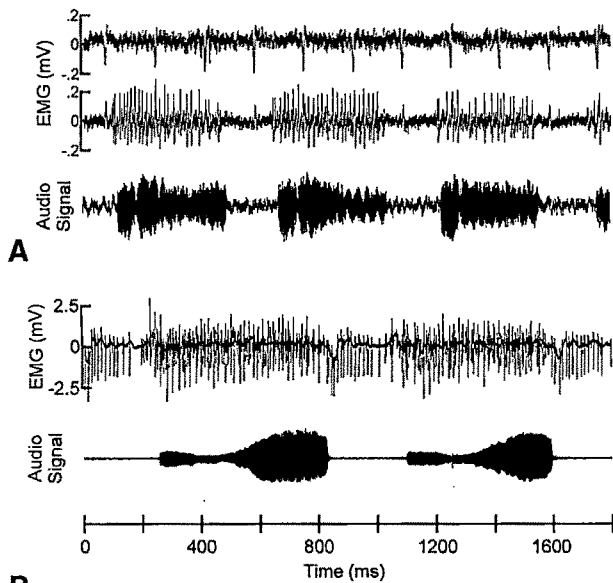


Fig 2. Electromyography (EMG) potentials recorded during vocalizations. A) Neck surface EMG recordings from above intact SH (top trace) or RLN-innervated SH (bottom trace) revealed vocal-related activity only in RLN-innervated SH. Three vocalizations are shown. Periodic spikes in top trace are of cardiac origin. B) Hooked-wire EMG recording from RLN-innervated SH shows different motor unit activity patterns correlated with 2 vocalizations and intervening periods of inspiration.

hooked-wire or needle electrodes. Vocal-related motor units typically began firing 15 to 65 ms before phonation and maintained a steady or slightly decrementing discharge throughout the phonation. The relationship between EMG potentials and specific vocal parameters is complex and will be presented in greater detail as a separate report.

Respiratory-Related EMG Potentials From RLN-Innervated SH. The EMG potentials correlated with respiration were recorded from the neck surface above the RLN-innervated SH in 7 of the 8 animals tested, starting as early as 4 weeks after surgery. Respiratory-related activity was recorded directly from the SH in the terminal experiments in all 8 animals. The EMG activity was predominantly inspiratory and was greatest during increased effort such as sniffing or when the airway was occluded (Fig 3A). Occasionally, we recorded from a mixture of clearly identifiable inspiratory and expiratory motor units (Fig 3B). Respiratory-related units were not observed when we recorded directly from the normal SH or from the SH of control animals. However, some relatively weak activity correlated with respiration was recorded from the neck surface above the right and left SHs in 2 control animals during airway occlusion.

Reflex Activity in RLN-Innervated SH Evoked by Mechanical Stimulation of Larynx. Large bursts of activity in the RLN-innervated SH were easily evoked in all nerve-transposed animals when a thin tube was inserted to stimulate the mucosa of the glottis. As shown for 1 representative animal in Fig 4, a similar simultaneous response could be recorded from the contralateral thyroarytenoid muscle in all 6 animals tested in this manner. Moreover, in 2 animals, we noted that when a larger-diameter plastic tube, roughly two-thirds the diameter of the trachea, was inserted transorally into the glottis, it often caused an inhibition of inspiratory-related units in the RLN-innervated SH (Fig 5A). This also occurred when the vocal folds were mechanically stretched or pressed with

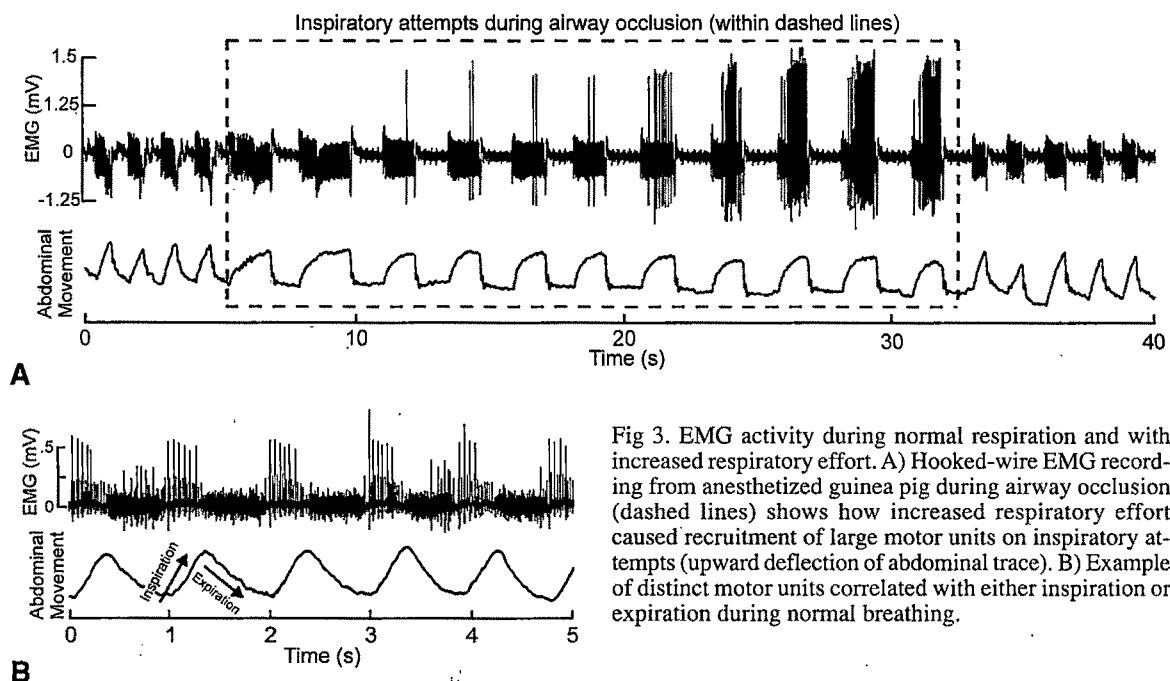


Fig 3. EMG activity during normal respiration and with increased respiratory effort. A) Hooked-wire EMG recording from anesthetized guinea pig during airway occlusion (dashed lines) shows how increased respiratory effort caused recruitment of large motor units on inspiratory attempts (upward deflection of abdominal trace). B) Example of distinct motor units correlated with either inspiration or expiration during normal breathing.

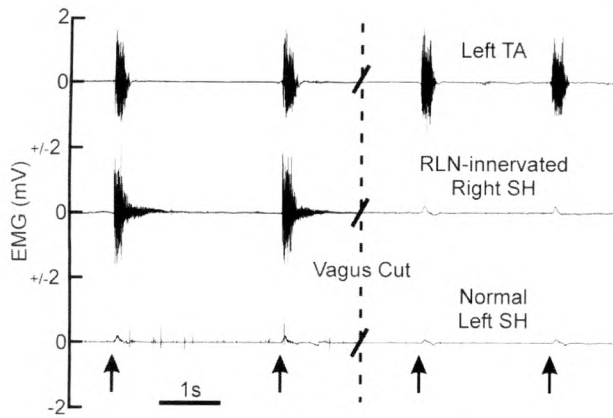


Fig 4. Bursts of EMG activity were elicited from RLN-innervated SH and contralateral thyroarytenoid muscle (TA) when laryngeal mucosa was mechanically irritated with thin plastic tube inserted into glottis. (Arrows indicate pokes.) Two reflex responses are shown both before and after vagus nerve was cut. Recordings were separated by approximately 20 seconds. Cutting right vagus nerve eliminated responses from ipsilateral SH.

a probe after the laryngeal lumen was exposed via an anterior midline laryngofissure. Pressing or stretching the vocal folds appeared to facilitate expiratory activity in both the intact thyroarytenoid muscle (not

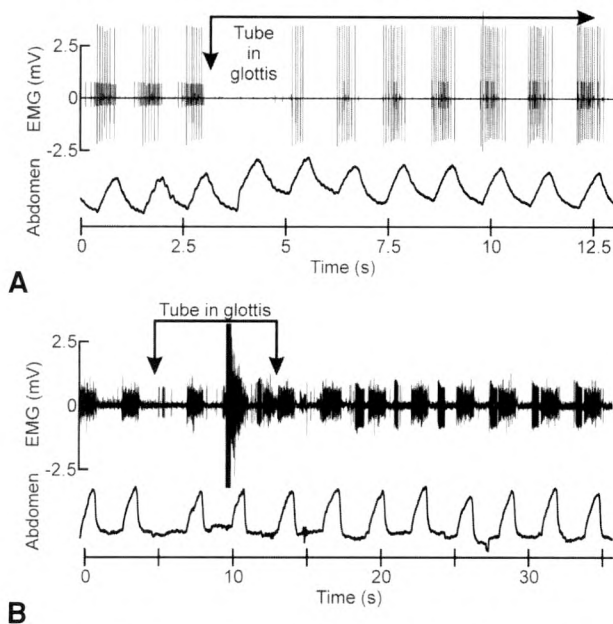


Fig 5. EMG potentials in RLN-innervated SH were affected by pressing, stretching, or otherwise mechanically stimulating vocal folds. A) When flexible tube two-thirds of diameter of trachea was inserted into glottis, it would stretch vocal folds and typically cause transient inhibition of inspiratory-related units. Note brief strong inhibition of motor units despite continued respiration. B) Insertion of large-diameter tube into larynx would sometimes elicit laryngeal closure ("gag") reflex. Such laryngeal stimulation occasionally elicited expiratory-related motor units that were not otherwise present. Observe EMG bursts appearing between inspirations (upward deflections of abdominal trace) after tube was inserted and removed.

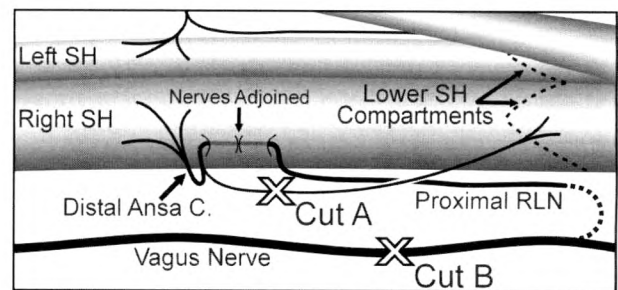
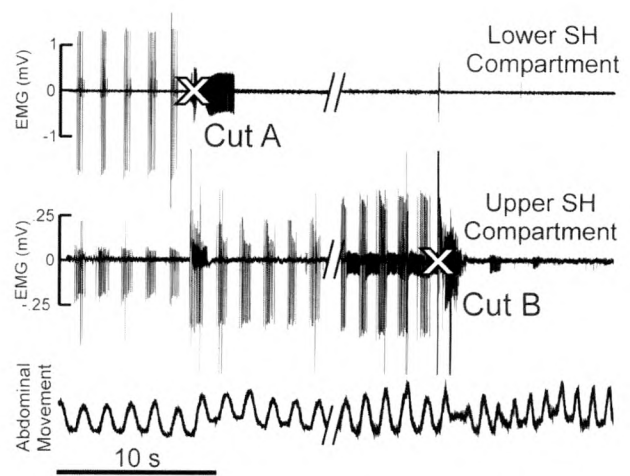


Fig 6. Nerve cuts confirmed RLN innervation of right SH. In 2 guinea pigs, it was possible not only to confirm RLN innervation of SH by cutting vagus or RLN nerve, but also to demonstrate that nerve end abutment successfully formed functional sutureless neurorrhaphy. One representative animal is shown in which respiratory-related EMG potentials from lower SH compartment (top trace) ceased after cutting of distal ansa branch feeding lower compartment (Cut A). Subsequent cut of right vagus (Cut B) denervated upper compartment. Break between recording traces represents pause of approximately 2 minutes.

shown) and in the RLN-innervated SH (Fig 5B). Cutting the ipsilateral vagus nerve or RLN abolished these responses to mechanical stimulation, as well as ongoing respiratory-related activity (Fig 6).

Evidence for Nerve Reinnervation Through Sutureless Neurorrhaphy. The guinea pig SH has a large upper compartment attached to the hyoid bone and a smaller lower compartment attached to the sternum (Fig 1). A similar subdivision is also found in the human SH.⁹ These compartments are consistently innervated by different nerve branches in the guinea pig (Fig 1). We observed in several normally innervated SH muscles that stimulation of the ansa cervicalis nerve branch feeding one compartment did not elicit EMG potentials in the other compartment. It was possible to isolate the small nerve branch of the distal ansa cervicalis supplying the lower compartment of the RLN-innervated SH in 2 guinea pigs during the terminal experiments. Cutting this small nerve branch abolished activity in the lower compartment

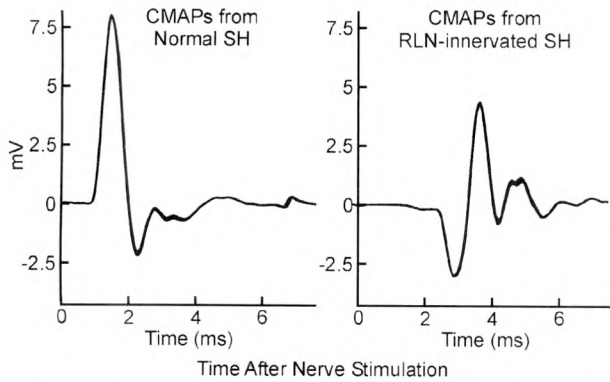


Fig 7. Compound muscle action potentials (CMAPs) from 1 representative guinea pig are compared for normal SH (ansa cervicalis stimulated) versus RLN-innervated SH (right RLN stimulated). Each plot contains 10 overlaid responses.

(Fig 6), indicating that the RLN had reinnervated the lower compartment through this branch in at least these 2 animals.

CMAPs Evoked by Stimulation of Vagus or Transposed RLN. We evoked CMAPs in the right SH by stimulation of the transposed RLN (Fig 7) and in the left SH by stimulation of the ansa cervicalis. Multiple paired *t*-tests (2-tailed, $\alpha = 0.05$) comparing normal (left) and RLN-innervated (right) SHs failed to find significant differences in the number of CMAP peaks, the rise time to the first CMAP peak, or the CMAP duration. However, the average biphasic CMAP amplitude was approximately twice as large for the naturally innervated left SH (mean, 23.9 mV) as for the RLN-innervated right SH (mean, 12 mV; $p < .05$, $df = 6$, $t = 2.45$), and the latency from stimulation to start of CMAP response was significantly shorter for the naturally innervated SH (mean, 1 ms) than for the RLN-innervated SH (mean, 1.7 ms; $p < .05$, $df = 6$, $t = 5.36$).

Stimulation of the RLN or the cervical vagus on the nonreinnervated side did not elicit SH CMAPs, even at very high stimulation levels. Regeneration of the right ansa cervicalis was observed in only 1 of the 8 nerve-transposed animals (No. 11). Stimulation of the regenerated ansa cervicalis in this animal evoked CMAPs in the right SH (but not the left SH), indicating that the cut ansa cervicalis had regenerated to some degree. Stimulation of the RLN also evoked CMAPs in the right SH of this animal, suggesting that this muscle had a dual innervation from the ansa cervicalis and the right RLN. Muscle fiber histochemistry also suggested a dual innervation for this animal's right SH (see next section).

Muscle Fiber Histochemistry. The RLN-innervated SH appeared conspicuously darker red in color than did the intact SH in most experimental animals. This

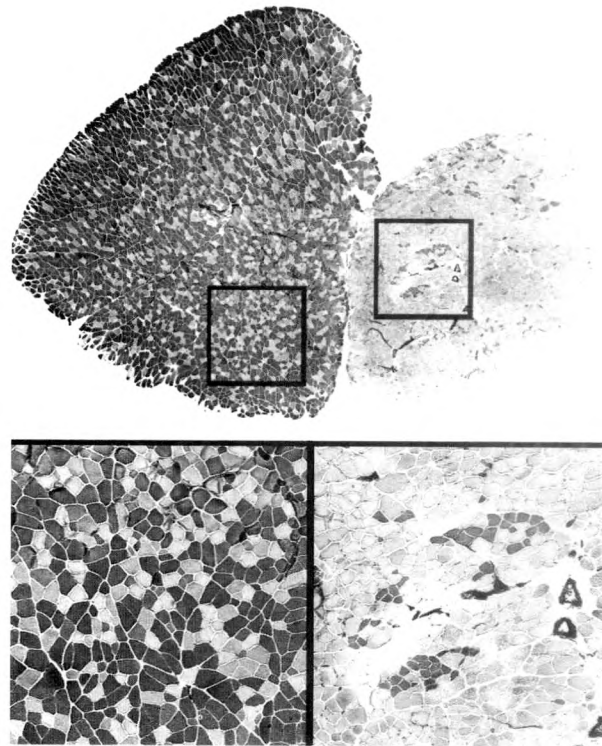


Fig 8. Photomicrographs of right and left SH muscles stained for adenosinetriphosphatase (ATPase; pH 4.6). Fiber type 1 stained medium gray, type 2b stained dark gray, and types 2a and 2x stained light. Magnified areas show mixture of fiber types for normally innervated SH (left), but only small clusters of type 1 fibers surrounded by type 2a and 2x fibers for RLN-innervated SH (right). Note relative absence of fatigable fibers (type 2b) in RLN-innervated SH. Fiber typing was performed in reference to serial sections stained with both ATPase and succinate dehydrogenase histochemistry. Magnified areas are 1.44 mm wide.

difference was likely a result of a higher concentration of myoglobin in the RLN-innervated SH, because SDH staining was strikingly more intense in the RLN-innervated SH than in the contralateral SH for the 4 animals histologically processed. In addition, the RLN-innervated SH was clearly smaller in diameter than the contralateral (intact) SH in each animal. The average cross-sectional area of the RLN-innervated SH was 49% that of the contralateral SH for the 4 animals sampled (Fig 8). Because the RLN-innervated SH had a reduction of only 22% in total number of muscle fibers compared to the naturally innervated SH ($p < .05$, $df = 3$, $t = 4.5$), yet a reduction of approximately half in surface area, it is possible that both fiber loss and an average reduction in fiber diameter contributed to the overall difference in muscle cross-sectional area.

The muscle fiber typing in the 4 processed guinea pigs revealed fiber type grouping in the RLN-innervated SH. The ATPase histochemistry revealed that type 1 fibers stained darker than type 2 fibers at pH

4.3. This pattern was reversed at pH 10.4. At pH 4.6, type 2 fibers could be subdivided into darker-staining type 2b fibers versus the lighter-staining 2a and 2x fibers. The reaction product densities for SDH histochemistry likewise distinguished the fatigue-resistant fibers (types 1, 2a, and 2x) from the fatigable fibers (type 2b), with the former staining conspicuously darker than the latter.

Three of the 4 animals demonstrated a dramatic difference in the percentage of fatigue-resistant fibers between the right and left SHs, with the intact side having an average of 30% type 2a or 2x fibers ($SD = 6\%$) and the RLN-innervated side having an average of 83% type 2a or 2x fibers ($SD = 11\%$). Figure 8 shows the typical appearance of the right and left SHs for these 3 animals. One of the 4 animals (No. 11), however, did not demonstrate a similar asymmetry in SH fiber types, having 31% type 2a or 2x fibers in the RLN-innervated SH and 22% type 2a or 2x fibers in the intact SH. Interestingly, this was the only animal in which the ansa cervicalis had clearly reinnervated portions of the denervated SH, a finding that possibly explains the relative lack of fiber type asymmetry.

DISCUSSION

We performed unilateral RLN transpositions in 8 guinea pigs by sectioning the right RLN and directing the proximal end to the ipsilateral denervated SH to explore the feasibility of recovering laryngeal neuromotor signals after laryngectomy. By comparing the spontaneous and elicited activity of the RLN-innervated SH with that of the normal contralateral SH, we found evidence that the transposed RLN had innervated the host SH in all 8 animals. Differences in muscle fiber typing between the operated and control SHs were also consistent with RLN innervation of the host SH.

EMG Potentials From RLN-Innervated SH. The successful innervation of the denervated SH by the transposed RLN in each of our guinea pigs is not surprising, given that a denervated skeletal muscle will accept innervation from basically any cholinergic motor nerve.^{10,11} It is noteworthy, however, that there was some evidence for the reestablishment of recruitment based on motor unit size in the RLN-innervated SH. When animals exerted greater respiratory effort, such as during airway occlusion, relatively large motor units often appeared within the ongoing bursts of respiratory-related EMG potentials from the RLN-innervated SH (Fig 3A). Previous work has shown that when a muscle is reinnervated by its original nerve supply, it is possible to reestablish a normal recruitment pattern of motor unit size and force.¹²

Orderly recruitment by unit size can also be reestablished if motor axons innervate synergistic muscles, but orderly recruitment is not always reestablished when a nerve is directed to an antagonistic muscle.¹³ The effort-related EMG potentials obtained in the present report indicate that the SH is a suitable host for reestablishing motor unit size for at least abductory laryngeal units in guinea pigs. Size-based recruitment would be useful if transposed EMG potentials are to be used for prosthetic control.

The EMG potentials recorded from the RLN-innervated SH correlated with both laryngeal abductory events (eg, inspiration) and adductory events (eg, swallowing, laryngeal closure reflex, and vocalization). This is expected, considering that several laryngeal muscles are normally supplied by the RLN. Axons that previously innervated the TA, for example, would be expected to fire during vocal fold adduction, whereas axons that previously innervated the posterior cricoarytenoid muscle would fire during abduction. Laryngeal activity involving the alternation of laryngeal adduction and abduction, such as a series of phonations separated by inspiration, could therefore generate a nearly continuous stream of activity in an RLN-innervated host muscle (Fig 2B). This could present problems in using the gross EMG signal for turning a prosthetic sound source on and off or modulating its pitch.

Individual motor units associated with either inspiration or expiration could often be identified in EMG recordings of the RLN-innervated SH on the basis of unit size and/or profile. If the same holds true for transposed laryngeal motor units in humans after laryngectomy, it may be possible to extract functionally meaningful information despite potential overlap of antagonistic activity in the host muscle EMG. However, in approximately 43% of adult humans, the RLN divides into multiple branches before entering the larynx.¹⁴ In these instances, the surgeon may be able to selectively transpose individual RLN branches to separate host muscles, thereby separating axons supplying laryngeal adductors (the anterior RLN branch) from those supplying laryngeal abductors (the posterior RLN branch) without entering the diseased larynx. Such anatomic separation of functionally distinct sources of motor supply would greatly simplify the task of extracting and interpreting vocal-related signals for prosthetic control.

CMAPs in RLN-Innervated SH. Stimulation of the transposed RLN or ipsilateral vagus nerve resulted in CMAPs that were reduced in amplitude (by about 50%) and longer in latency compared to those elicited in the contralateral muscle by stimulating its natural source of innervation (Fig 7). The average

CMAP biphasic peak amplitude was approximately 50% smaller in the RLN-innervated SH compared to the contralateral SH. The reduced CMAP amplitude was likely related to muscular atrophy, because there was a corresponding reduction by approximately 50% in average cross-sectional area of the RLN-innervated SH for the 4 animals examined. The longer latencies could be a result of the decrease in internode length associated with regenerated axons¹⁵; however, it is also possible that differences in nerve length from the point of stimulation to the recorded muscle contributed to the differences in CMAP latency.

Muscle Fiber Histochemistry. The RLN-innervated SH had muscle fiber populations remarkably different from those of the contralateral SH, as shown by ATPase and SDH histochemistry (Fig 8). This relative shift from fast fatigable (type 2b) to fast fatigue-resistant (types 2a or 2x) fibers could be a result of increased muscle activity associated with RLN innervation. It is well established that muscle fiber phenotype is flexible and largely determined by patterns of activation after birth.^{16,17} It is likely, therefore, that the continuous respiratory-related contractions imposed by the transposed RLN caused the host SH to become predominantly fatigue-resistant, thereby more closely resembling the fiber type constituency of laryngeal^{18,19} rather than strap muscles.²⁰ Control experiments in which the SH is reinnervated by its own motor nerve must be conducted before the dramatic change in fiber type observed in our animals can be unequivocally attributed to RLN innervation.

Comparison With Previous Vagus Nerve Transposition Studies. Several investigators over the past century have transposed the vagus nerve to a wide variety of skeletal muscles. It has been shown that if the proximal vagus nerve is transposed at the cervical level before the branching of the RLN, then the host muscle will spontaneously contract coincident with laryngeal activity.^{10,21,22} For example, Reichert²² performed unilateral vagus nerve transposition in 5 dogs, connecting the proximal vagus cut at the level of the thyroid gland to the cut distal end of the ipsilateral hypoglossal nerve. After 11 to 16 weeks of recovery, localized regions of the ipsilateral tongue in each dog contracted during inspiration, expiration, swallowing, coughing, or chemically induced vomiting. As in our study, the strength of these tongue contrac-

tions was related to the level of effort. The presence or absence of contractions correlated with phonation was not reported.

Potentials specific to laryngeal function have also been obtained in both animal models and human patients after RLN transposition. Guth et al²³ unilaterally transposed 1 RLN to the ipsilateral denervated hemidiaphragm by neuroorrhaphy to the phrenic nerve in rats and monkeys. They demonstrated that the RLN is capable of functionally innervating the paralyzed hemidiaphragm. Other reports demonstrate that the proximal phrenic nerve can be directed to the laryngeal abductor muscles to appropriately reanimate the paralyzed larynx for respiration.^{24,25} In both cases, functional reanimation is likely attributable to the naturally synchronous firing patterns of the 2 nerves during inspiration.²¹

In humans, Herrmann⁴ demonstrated that the RLN can innervate a neck strap muscle by transposing the RLN to the SCM during laryngectomy in 7 patients. His goals were very similar to ours, in that he wanted to obtain residual laryngeal vocal motor signals from host strap muscle EMG and use these signals to control a prosthetic speech aid. He proposed using laryngeal EMG potentials from the host muscle to control a stoma valve for hands-free tracheoesophageal speech. Although Herrmann was successful in obtaining EMG potentials correlated with vocal attempts in his patients, we have failed to find mention of these EMG signals' being applied to prosthetic control in the decade since his report.

Few details were provided by Herrmann⁴ regarding the transposed EMG potentials obtained in his laryngectomy patients. Provided that transposed laryngeal EMG potentials adequately resemble normal activity patterns, it may be possible to extract key vocal parameters from host muscle EMG and apply them for improved control over voicing parameters of prosthetic speech aids such as the EL or the opening and closing of a stoma valve for tracheoesophageal speech. The present findings in guinea pigs indicate that neck strap muscles can serve as host muscles for obtaining neck surface EMG recordings of transposed laryngeal motor signals. Human trials of RLN transposition during laryngectomy are in progress to explore the extent to which such signals can be used for improving prosthesis-aided speech.

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TRACHEAL RECONSTRUCTION WITH POROUS HIGH-DENSITY POLYETHYLENE TRACHEAL PROSTHESIS

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The variety of methods used for the treatment of severe tracheal stenosis and the occasional failure to obtain lasting and consistent relief are measures of the difficulty of the problem. Presently, several surgical approaches are used for reconstructing large defects of the cervical trachea, reminding us that no single technique has gained wide clinical acceptance. We resected a U-shaped cartilage from 6 to 8 rings of the trachea of 10 New Zealand rabbits. We used a porous high-density polyethylene (PHDP) prosthesis to reconstruct the cervical trachea, and did not perform a tracheotomy during this operation. We followed up the rabbits for 4 to 10 months. One of the rabbits died in the second month because of respiratory distress; another was lost in the fourth month of the study while delivering young. The others continued to thrive; in fact, one of them gave birth 3 times after our study and was well able to take care of her young. At the end of the study, the rabbits were painlessly sacrificed in order to remove the larynx and trachea and examine them histopathologically. In the histopathologic examinations, the prostheses were incorporated into the native trachea and adhered to the surrounding organs, especially to the esophagus. No mucosal irregularities were seen on the surface of the prosthesis, and all the surfaces appeared to be covered with ciliated pseudostratified epithelium. This tracheal prosthesis provides good results in rabbit tracheal reconstruction, and appears very promising for the clinical repair of tracheal defects.

KEY WORDS — porous high-density polyethylene, reconstruction, trachea.

INTRODUCTION

Reconstruction of tracheal defects is performed after tissue extirpation in cancer or resection of stenotic regions, and an end-to-end anastomosis is now considered to be the method of choice for defects of up to approximately 6 cm in adults.¹⁻³ However, in the case of larger defects, another method of reconstruction is required. Researchers, encouraged by the success of artificial vascular grafts, have developed a variety of tracheal prostheses made of synthetic biomaterials. Most techniques involve multiple stages carried out over an extended period of time; tubular prosthetic materials, which have become so customary in the realm of vascular surgery, have not proven equally effective in reconstruction of defects of the trachea.

Successful prosthetic reconstruction of the trachea requires fulfillment of several criteria,⁴ including providing a flexible yet noncompressible airway, complete incorporation of this structure into the recipient's surrounding tissue, epithelialization of the lumen to achieve effective removal of tracheobronchial secretions, and being clinically stable and noncarcinogenic.

For these reasons, in this study we used a porous

high-density polyethylene (PHDP) prosthesis that is biocompatible and flexible, being easily shaped and sutured and applicable in a single operation for tracheal reconstruction.

MATERIALS AND METHODS

The prosthesis used in this study was manufactured from a linear PHDP (Medpor Biomaterials, Por-ex Surgical Inc, College Park, Ga). This PHDP is constructed purely of medical-grade, high-density polyethylene, which is a highly inert material with a long history of use in the craniofacial skeleton.^{5,6} Clinically, more than 30 years of patient follow-up are reported, attesting to its high biocompatibility.⁷ Unlike other porous alloplasts, which are held together with potentially bioreactive plasticizers, PHDP is heat-welded or sintered together to create a pure framework of interconnecting, omnidirectional pores with an average pore size of greater than 150 μ m and a pore volume of 50%.^{8,9} This rather unique composition enables tissue fluids to circulate throughout the implant, allowing rapid vascularization and accompanying rapid soft tissue ingrowth.

Remarkably stable, PHDP is insoluble in tissue fluid and elicits virtually no foreign body response.

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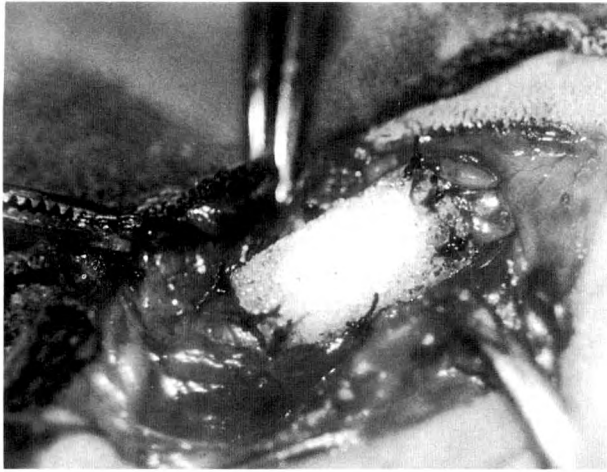


Fig 1. Photograph taken after tracheal segment was replaced with tracheal prosthesis.

It has a high tensile strength that resists compression, thereby protecting the pore size. It is strong yet somewhat flexible, while sufficiently rigid to maintain its structural integrity. The implant is easy to shape and carve; further, it can be molded simply by placing it in hot saline solution and forming it into the desired shape. When implanted, the material becomes surrounded by a thin, fibrous, loose connective tissue capsule that does not undergo contracture and has no adverse effect on the overlying soft tissue. In more than 30 years of clinical use, there has been no evidence of carcinogenesis.⁷

In this study, a preformed tracheal prosthesis was fashioned from sterile PHDP in the form of 0.85-mm-thick material (Medpor catalog No. 7219). The thin sheet was cut into a rectangle of the same dimensions as the resected tracheal piece. The implant was then set in boiling water for several minutes and cooled over a cylindrical surface to provide it with a semilunar curvature.

Four female and 6 male New Zealand rabbits weighing 1.77 to 2.65 kg were anesthetized by intramuscular injection of ketamine hydrochloride (80 mg/kg) and xylazine hydrochloride (8 mg/kg). The rabbits were stabilized in the supine position, and the neck skin was shaved and prepared with povidone iodine solution. Under spontaneous respiration, the cervical trachea was exposed through a midline incision in the neck by dissecting the strap muscles. A segment of the trachea including 6 to 8 tracheal cartilage rings was resected in a U-shape in the lower cervical trachea. A tracheal prosthesis was well soaked with rabbit blood, and then the prosthesis, bent and shaped according to the shape of the resected piece of trachea, was sutured in place of the defect with 6-0 Vicryl (Ethicon) sutures (Fig 1). Upon completion of the reconstruction, a drain set was applied near

the trachea, and the cervical incision was closed layer by layer.

Cefazolin sodium was given intramuscularly at a dose of 10 mg/kg (2 times per day) for 5 days. A single dose of methyl prednisolone sodium succinate was given intramuscularly at a dose of 2 mg/kg on the day of the operation. The animals started to eat and drink 2 hours after the operation, and their drains were removed on the third day. The sutures were removed on the seventh day.

The tracheas of the animals were followed up radiologically after the operation with magnetic resonance imaging (MRI), high-resolution computed tomography (CT), and spiral CT.

In the postoperative 4- to 10-month period, the animals were painlessly sacrificed with an overdose injection of sodium pentobarbital. The prosthesis was resected en bloc with both the distal and proximal sites of the native trachea, and after macroscopic examination the specimens were processed for light microscopic examination.

The animal protocol was approved by the Istanbul University School of Veterinary Medicine's Institutional Animal Care and Use Committee.

RESULTS

During the postoperative period, the rabbits were followed up daily. They were healthy in general and could carry on their normal daily activities and sexual life. During sexual intercourse, the rabbits were found to exert much effort and energy; however, no respiratory symptoms such as stridor were detected. The females were able to become pregnant, and 1 of them gave birth 3 times subsequently, thus maintaining her normal physiological functions. However, 1 of the female rabbits (rabbit 7) could not tolerate the excessive effort and burden of delivery and died while giving birth. Stridor was detected in 1 of the male rabbits (rabbit 4) just after the operation. The stridor gradually increased, the animal could not eat or drink and lost weight, and it was given euthanasia.

Because of the unexpectedly early deaths of 2 rabbits, their CT and MRI examinations could not be carried out. The macroscopic examination of the tracheas revealed dislocation at the left lateral border of the prosthesis of rabbit 7, the space between it and the trachea being filled with granulation tissue and the tracheal lumen being partially filled with this granulation tissue. The macroscopic examination of the trachea of rabbit 4 showed the prosthesis partially dislocated from the trachea and granulation tissue filling these dislocation spaces. The tracheal lumen of rabbit 4 was observed to be almost totally obstructed

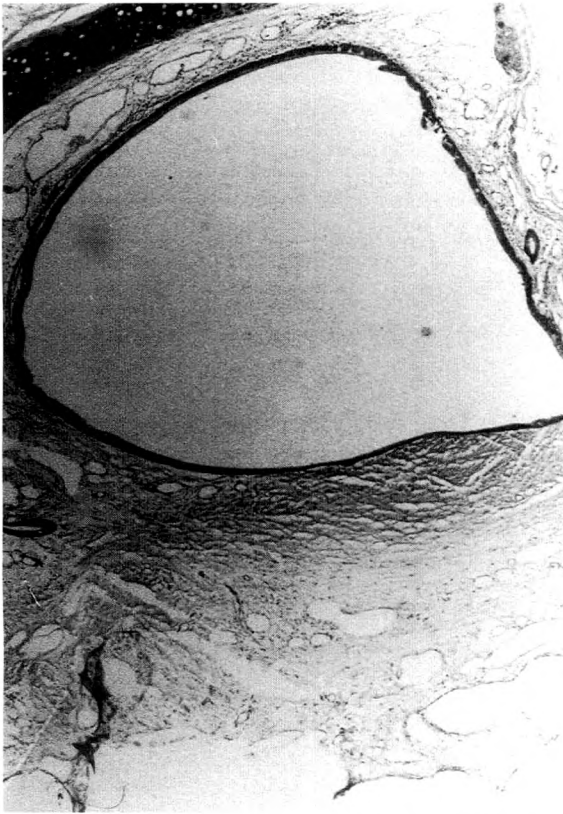


Fig 2. Epithelial lining of graft is atrophic in appearance, and demonstrates submucosal fibrosis and slight lymphoplasmocytic infiltration (H & E, original $\times 40$). Lumen is regular in shape.

by the granulation tissue.

The remaining 8 rabbits survived with no evidence of infection, rejection, or extrusion of the prostheses. They were painlessly sacrificed 2 at a time at 4, 6, 8, and 10 months.

The postoperative courses were uneventful for the surviving 8 rabbits. The prostheses were incorporated into the native trachea and adhered to the surround-

ing organs, especially to the esophagus. However, no erosion was observed in the vessels to which the prostheses had adhered. The luminal surface was almost entirely covered with the host tissue, and no irregularities were observed. The light microscopic examination showed that connective tissue, including small vessels, had invaded the pores and that a layer of connective tissue had covered the prostheses. Ciliated pseudostratified epithelium was seen in the inner layer of the trachea. Slight atrophy of the epithelium was seen to have developed on the prosthesis surface. In some places, there were focal and slight infiltrations of lymphocytes, plasmacytes, and polymorphonuclear leukocytes (Figs 2 and 3).

The 2 rabbits that died in the second and fourth months after reconstruction were examined histopathologically. Dislocation was present in a single area in the prostheses. Granulation tissue was noted at the reconstruction site in the trachea and in the lumen of the trachea (Fig 4).

The MRI, CT, and spiral CT findings of the 8 sacrificed animals were evaluated 1 week before sacrifice. The sections of the neck examined on CT were taken axially as 5 mm in width and around the actual reconstruction region as 3 mm in width. The reconstruction region was followed for 10 to 15 mm, and no obstruction or stenosis was detected (Fig 5).

In spiral CT examinations, the reconstructed region of the trachea was observed to become ovoid, but the mucosal surface was intact, with no stenosis of the lumen (Fig 6). On MRI examination, partial flattening of the curve was observed in the prosthesis; however, no obstruction was observed in the lumen (Fig 7).

DISCUSSION

Tracheal defects resulting from extensive head and

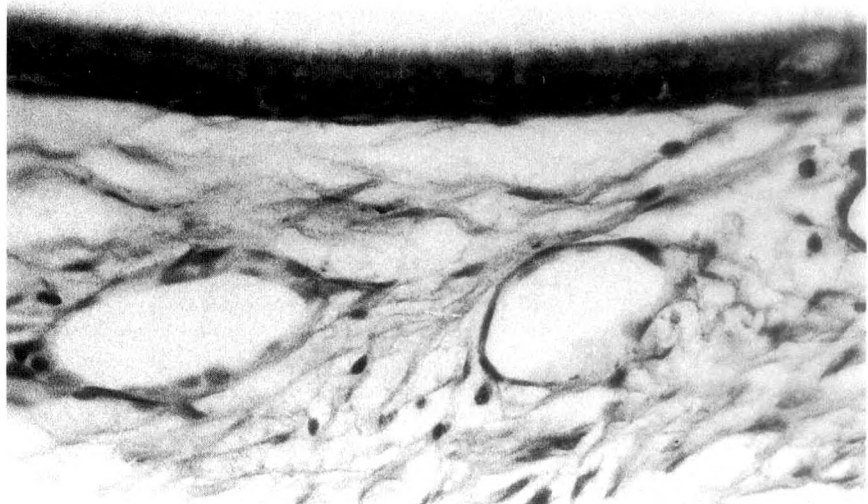


Fig 3. Note presence of ciliated pseudostratified epithelium lining surface of prosthesis (H & E, original $\times 250$).

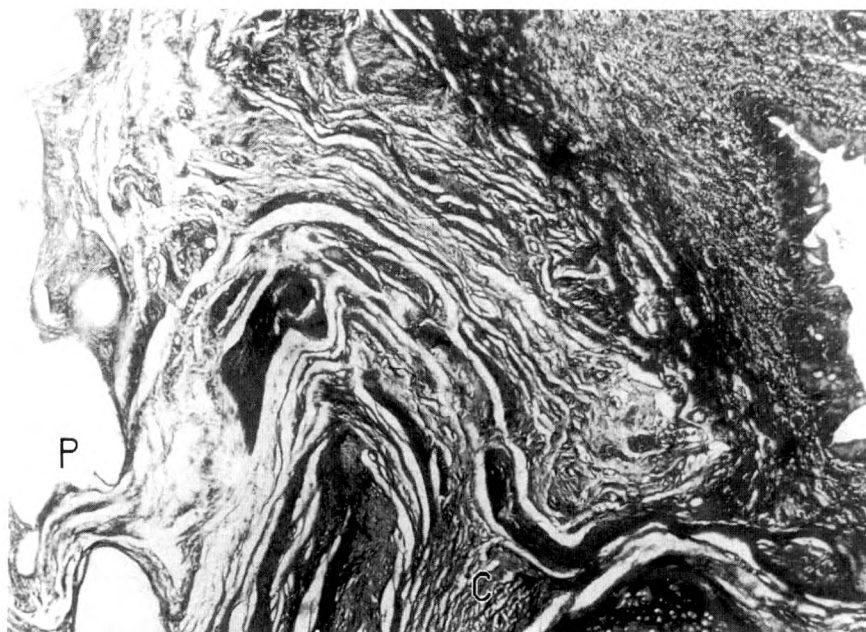


Fig 4. Intratracheal granulation tissue in rabbit 7 (toluidine blue, original $\times 100$). P — prosthesis, C — cartilage.

neck cancer surgery or acquired from blunt trauma or prolonged endotracheal intubation can be a devastating clinical entity. Rehabilitating patients to a state of normal respiratory and phonatory function poses a formidable challenge to the contemporary head and neck reconstructive surgeon. Presently, several surgical approaches are used in reconstructing large defects of the cervical trachea, reminding us that no single technique has gained wide clinical acceptance.

It is well recognized that primary end-to-end closure without excessive tension represents the ideal method of reconstructing tracheal defects.¹ Clinical experience has shown that defects of up to 3 cm can ordinarily be repaired by mobilization of the distal trachea with end-to-end reapproximation¹⁰; larger defects, on the order of 6 to 7 cm, can also be closed by this method, but require additional intrathoracic lengthening. Such techniques have been proved suc-

cessful, but are not without significant morbidity.¹

Probably the most successfully used technique for reconstructing large tracheal defects is the “trough” method originally reported by Fairchild¹¹ in 1927 and later popularized by the pioneering work of Lawson et al,¹² Biller et al,¹³ and others.¹⁴⁻¹⁶ A trough is formed by advancing laterally based skin flaps toward the removed stenotic tracheal segment; if possible, the posterior tracheal mucosa is retained. Next, semirigid or rigid materials are inserted subcutaneously, adjacent to the trough. The third stage involves rotating a medially based cervical skin implant flap to recreate the anterior tracheal wall, which is covered with a local cervical rotating flap. The most frequently used material has been Marlex mesh^{10,12,13,15}; however, other materials have been tried, including nasal cartilage,¹⁷ rib cartilage,¹⁸ tantalum mesh,¹⁰ and plastic (polypropylene) rings.^{1,16} The disadvantages of this technique include multiple operations staged over an extended period of time.

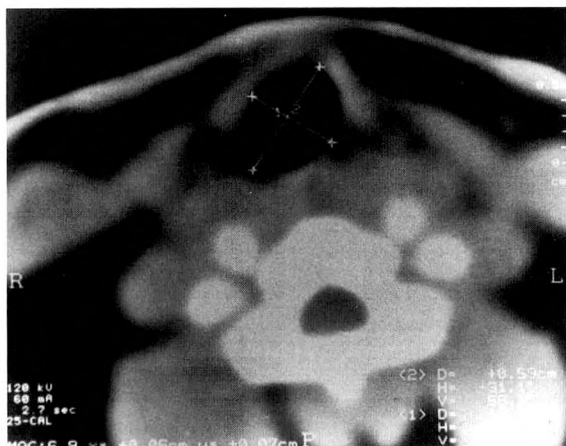


Fig 5. Axial computed tomography scan shows no obstruction in tracheal lumen of rabbit 9.

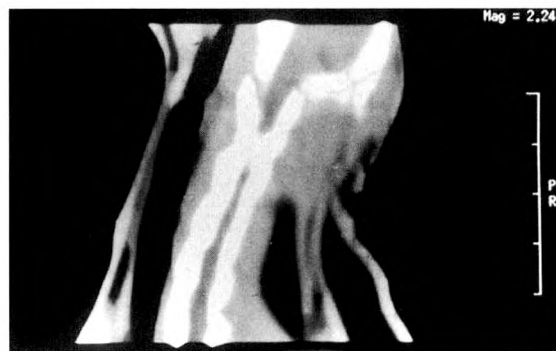


Fig 6. Spiral computed tomography scan shows tracheal lumen of rabbit 8. Mucosal surface is intact, with no stenosis of lumen.



Fig 7. T1-weighted axial magnetic resonance image shows no granulation tissue of tracheal lumen of rabbit 1.

Larger defects usually require local myocutaneous or distant pedicled flaps. Eliachar et al^{19,20} have championed the "rotary door" myocutaneous flap for anterolateral tracheal defects. Other investigators have examined the utility of pedicled flaps, including the platysma,^{21,22} pectoralis major,²¹ latissimus dorsi,²³ myo-osseous intercostal flap,²⁴ and omental flap,²⁵ all with limited success. Microvascular free flaps have also been used, including radial forearm flaps,²⁶ composite temporoparietal fascial flaps,²⁷ jejunum,²⁸ and even prefabricated, hormonally induced autografts.²⁹

Alloplastic replacement of large tracheal defects has not met with the same success as reconstruction of small defects performed with autogenous material. Encouraging work by Kaiser³⁰ demonstrated that small (2×2 cm) anterior defects could be successfully repaired by patches of large-pore polyurethane that became incorporated and epithelialized by 90 days. However, observing larger (4×4 cm) circumferential defects repaired by nonwoven polyurethane, Schauwecker et al³¹ demonstrated that although the alloplast did become incorporated into surrounding connective tissue, it stenosed because of intraluminal granulation tissue. In 2 studies investigating the application of polytetrafluoroethylene, it was found that although the material was well tolerated, it did not become incorporated into the trachea, nor did it develop any respiratory epithelium.^{32,33} Similar attempts at reconstructing large tracheal defects with other free alloplasts, such as Proplast,³⁴ hydroxyapatite,³⁵ Teflon,³⁶ and nonvascularized homografts, including preserved homologous aorta and trachea, have met with the same disappointing results.³⁶

The most promising results seem to involve a combination of techniques in which an alloplastic mate-

rial is coupled with an autogenous carrier, forming a vascularized composite reconstruction unit. Har-El et al,³⁷ working with methylmethacrylate, demonstrated that by initially conjoining the alloplast with a myocutaneous flap, they could achieve survival of the composite unit and epithelialization of the reconstructed tracheal segment. Inspiring clinical work by Lindholm and Löfgren³⁸ with porous polytetrafluoroethylene and pyrolyzed carbon showed great success in laryngotracheal reconstruction in 3 cases in humans. Their 3-stage technique involves initial formation of a paralaryngeal mucosa, autogenous cyst that is incorporated into a composite polytetrafluoroethylene-muscle mucosa reconstruction unit. The success of these composite techniques appears to rest on the ability of the alloplast to become vascularized and incorporated into surrounding tissue — a property distinctive to porous materials.

In this study we used PHDP material prostheses in a single operation without tracheotomy. The PHDP is a biocompatible material that is hard enough not to collapse. It can be cut and bent easily to take the shape of the defect and can easily be sutured. We resected a wide U-shaped piece of trachea in the frontal wall. Then we cut a piece of PHDP of the same dimensions as the piece of trachea. We shaped it and sutured it in place. Postoperative examination revealed the trachea and the prosthesis to be in a 1-piece, cylindrical shape. However, MRI, CT, spiral CT, and the histopathologic examinations revealed the prostheses to be somewhat flattened, though still allowing sufficient passage. Because the tracheas of rabbits are small, they were hard to manipulate, and especially hard to suture. For this reason, in 2 rabbits, dislocation and granulation tissue development occurred because of inappropriate (end-to-end) suturing of the cartilage and the prosthesis. These 2 animals died after the operation. We believe that this problem can be solved in humans, because they have larger tracheas, providing that the prosthesis can be preshaped and perforated for suture replacement previously.

Among the sacrificed animals, the macroscopic examinations revealed the trachea and the prosthesis to be 1 single piece, from both the inside and outside, and no irregularities of the mucosa were detected. In the examination of histopathologic samples, the mucosa of the trachea's lumen was seen to extend over the prosthesis also. The epithelium of the mucosa was ciliated pseudostratified epithelium and covered the whole surface of the prosthesis, although it was atrophic in focal areas.

Despite PHDP's advantageous properties, surprisingly little work has appeared in the literature regard-

ing its application to laryngotracheal reconstruction. The first published report pertaining to the use of PHDP for reconstructing a trachea was by Sauer and Lade,³⁹ who demonstrated the feasibility of using this material in conjunction with autogeneous materials. Joachims et al⁴⁰ reported their results with Plasti-Pore (Smith & Nephew, Richards, Bartlett, Tenn), an analog of PHDP (Medpor) with a smaller pore size, commonly used in prosthetic middle ear reconstruction. Although they were able to resurface the lumen with

a mucosal or split skin graft, there was inadequate incorporation of the alloplast.

The goal of this investigation was to assess the applicability and utility of PHDP in tracheal reconstruction. The results clearly demonstrate the utility of this alloplast as a bioacceptable material. In particular, PHDP lends itself extremely well to the complexities of tracheal reconstruction, especially when used in a staged, composite manner.

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IMAGING CASE STUDY OF THE MONTH PEDIATRIC TEMPORAL BONE FRACTURES

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INTRODUCTION

Temporal bone fractures in children are rare. Temporal bone fractures with an associated cerebrospinal fluid (CSF) fistula that does not resolve spontaneously are even more uncommon. The clinical presentation often consists of a hemotympanum and hearing loss, but diagnostic evaluation and treatment options often vary depending on the severity of the injury.

CASE REPORT

A 6-year-old child was struck in the right temporoparietal area of the skull by a falling truck tailgate. The child's skull was trapped between the tailgate and the ground. There was reportedly a brief loss of consciousness at the scene, but by the time of arrival at the University of Mississippi Pediatric Emergency Department, the patient, though lethargic, was responsive and cooperative. Physical examination revealed a superficial abrasion over the right temporal area, a temporoparietal subgaleal hematoma, and a right hemotympanum with an intact tympanic membrane and a normal external auditory canal. No other signs of basilar skull fracture were noted. Cranial nerve VII was grossly intact. A computed tomography (CT) study of the head with contiguous 7-mm axial sections revealed a linear parietal skull fracture extending from the vertex anteriorly to the coronal suture inferiorly, with an 8-mm depression of the right anterior temporal bone.

An otologic examination performed 4 weeks after discharge revealed a resolved hemotympanum with clear effusion in the right middle ear. The child complained of a significant hearing loss on the right side. An audiogram showed a moderate mixed hearing loss with a speech reception threshold of 80 dB. The effusion and complaint of hearing loss persisted, and 5 weeks after the accident the patient underwent diagnostic tympanocentesis, which confirmed the middle ear effusion to be CSF by β -2 transferrin analysis. An Omnipaque cisternogram was completed in an attempt to localize the exact site of the CSF fis-

tula. The cisternogram showed a transverse fracture through the right temporal bone, just lateral to the right jugular fossa. The fracture began posteriorly lateral to the jugular fossa and extended anterolaterally. The superior aspect of the fracture was located posteromedially to the cochlear aqueduct, traveled into the vestibule, and extended into the middle ear (see Figure). The ossicles appeared intact. The child underwent serial lumbar punctures with aspiration of CSF, but the fistula failed to close with nonsurgical treatment.

The patient underwent a right middle ear exploration to localize and patch the CSF fistula. A postauricular approach with elevation of the tympanic membrane released a large amount of clear fluid that persisted throughout the initial examination. The ossicles were uninjured. The stapes footplate was examined and appeared normal, without evidence of a fistula. Further examination revealed the round window to be the source of the CSF leak. The round window was packed with a temporalis muscle graft tamponading the fistula. The patient recovered from the operation without complication.

DISCUSSION

Temporal bone fractures in children are uncommon. Several studies have demonstrated that children suffer fewer injuries to the skull base than adults, likely because of the resiliency of the pediatric skull and the smaller face-cranium ratio exhibited by adults. A 12-year review of basilar skull fractures revealed 679 injured children, 147 (21.6%) of whom had temporal bone fractures.¹ Another review of temporal bone fractures revealed 122 patients, including 25 children (20.5%),² and a third review of pediatric maxillofacial trauma covered 4 years and evaluated 72 children, 12 (16.7%) of whom had temporal bone fractures.³ The causes of temporal bone fractures in children vary, with most series citing motor vehicle collisions as the most common cause (42% to 60%), followed by falls (27% to 50%). Blunt trauma accounts for a minority (0% to 8%) of cases.^{2,4-6}

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Coronal computed tomography scans of right temporal bone. A) Scan shows fracture entering medial aspect of vestibule (arrow). Note water-soluble contrast material in subarachnoid space of cerebellopontine angle cistern (arrowhead) that flows through fracture into vestibule (asterisk). B) Scan shows water-soluble contrast material in subarachnoid space (arrowhead) filling middle ear space. Note tympanic membrane (arrow); contrast material flows into external auditory canal through incision created during diagnostic tympanocentesis.

The complaint of hearing loss is particularly common among children with temporal bone fractures, with one series reporting 48% of affected children as having some degree of hearing loss.⁶ Patients with longitudinal temporal bone fractures that parallel the petrous ridge typically experience a conductive hearing loss as a result of hemotympanum, tympanic membrane perforation, or ossicular damage. Sensorineural hearing loss is more common with transverse fractures that run perpendicular or oblique to the petrous pyramid. However, a transverse fracture may disrupt the membranous and neural structures within the labyrinth or cochlea, resulting in vertigo and sensorineural hearing loss. Longitudinal fractures with conductive hearing loss have a relatively good prognosis for recovery.

The physical examination of a child with a temporal bone fracture may yield classic findings such as hemotympanum, which is the most common sign associated with a temporal bone fracture, or bleeding from the external auditory canal. Tympanic membrane perforation, CSF otorrhea or rhinorrhea, "raccoon eyes," Battle's sign, facial nerve paralysis, vestibular symptoms, and hearing loss all may mark the presence of a temporal bone fracture.⁷

Otorrhea of CSF as a result of a temporal bone fracture occurs infrequently, as well. One series of 147 children with temporal bone fractures included 37 (25%) with signs of a CSF fistula.¹ The fact that the majority of CSF fistulae spontaneously resolve makes the true incidence of CSF fistula occurrence impossible to determine. It is not uncommon for CSF

leaks to be intermittent or to have a latent period between injury and presentation. In one report, 25 of 30 cases (83%) of known CSF otorrhea ceased spontaneously within 5 days. Four more leaks closed over 7 to 10 days with the assistance of lumbar drains, yielding a 97% closure rate with nonsurgical measures.⁷ Conservative treatment consists of bed rest, head elevation, and avoidance of strenuous activity, and may advance to serial lumbar punctures with CSF aspiration or lumbar drain placement. In the uncommon event of a fistula's failing to close with conservative measures, more rigorous intervention is indicated.

Chemical analysis of fluid, either otorrhea or rhinorrhea, is indicated if the nature of the draining fluid cannot be definitively established. Glucose content (>0.4 g/L) and β -2 transferrin are well-established indicators of CSF. In fact, β -2 transferrin is pathognomonic for CSF.⁸

Localization of a temporal bone fracture is currently best accomplished with high-resolution CT. Infrequently, the use of water-soluble contrast injection for cisternography is incorporated to assist with the identification of a specific fistula site. Of 39 patients with temporal bone fractures, 7 (18%) had persistent CSF leaks after conservative therapy. Four of the 7 (10%) required cisternography to document the fistula.¹ However, it has been established that CT with or without the use of water-soluble contrast material has a very high yield of fracture demonstration; the illustration of the specific fistula site is somewhat less specific. In this situation, surgical exploration is

indicated.

Surgical intervention to repair a CSF fistula caused by a temporal bone fracture is exceedingly rare. Only 2 of the 147 cases (0.01%) referenced earlier required surgical intervention.⁷ Recognized indications for surgical intervention include a CSF leak that persists for 7 to 10 days, recurrent meningitis, development of a CSF leak after a latent period, dural herniation, and a large temporal bone defect.⁹

CONCLUSION

This case presentation describes the rare event of

a temporal bone fracture caused by blunt trauma in a pediatric patient. The case is made even more unusual by the presence of a CSF fistula through the round window that persisted for an extended amount of time in spite of conservative therapy. This child required a cisternogram coupled with a middle ear exploration with a temporalis muscle plug of the round window to stop the persistent CSF drainage. The child's clinical presentation of hemotympanum and persistent hearing loss is common among children with temporal bone fractures, but the type of injury and the treatment required to correct it establish the unique nature of this case.

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DIAGNOSIS AND DETERMINATION OF THE CLINICAL SIGNIFICANCE OF TYPE 1A LARYNGEAL CLEFTS BY GELFOAM INJECTION

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Laryngeal clefts are rare congenital disorders, classified by multiple different schemes. Type IA (Armitage) and type I (Benjamin and Inglis) laryngeal clefts exhibit absence or hypoplasia of the interarytenoid muscles with an intact cricoid ring. Submucous or "occult" clefts occur with intact mucosa but absent underlying cartilage and/or muscle. Children with a diagnosis of posterior laryngeal cleft often have other congenital anomalies or medical disorders, including gastroesophageal reflux, tracheomalacia, syndrome complexes, and developmental delay. These associated disorders often confuse the diagnostic picture, as they may contribute to or account for the presenting symptoms of a laryngeal cleft. We propose a method to help clarify the clinical significance of the laryngeal clefts in these patients, and determine which patients would benefit from cleft repair. Eight patients with type IA laryngeal clefts are presented who were treated with a "test dose" Gelfoam injection into the interarytenoid area at the time of endoscopic diagnosis. All patients exhibited clinical improvement, and 4 patients showed improvement on the postinjection videofluoroscopic swallow study as compared to preoperative studies. One patient has gone on to surgical repair of the cleft after multiple injections. Endoscopic Gelfoam injection at the time of diagnosis can both alleviate symptoms and provide clarification of the posterior laryngeal cleft's contribution to the clinical status of the patient in these often complex cases.

KEY WORDS — endoscopy, Gelfoam, laryngeal cleft.

INTRODUCTION

Laryngeal clefts, previously considered extremely rare, have recently been identified and reported more frequently, with better definition. The minor clefts, in particular, have appeared in the recent literature with descriptions of techniques for diagnosis and measurement.¹ Laryngeal clefts have been classified by many different schemes based on clinical and histopathologic findings. Armitage² classified clefts as follows: type I defects are limited to the cricoid cartilage; type IA is an interarytenoid cleft, extending to, but not into, the superior aspect of the cricoid; type IB clefts extend partially through the cricoid; and type IC clefts extend completely through the cricoid. Armitage type II clefts include the proximal 3 cm of the tracheoesophageal septum, and type IV involves the entire septum. The Benjamin and Inglis³ classification system considers a supraglottic cleft to the superior aspect of the cricoid cartilage type I; clefts of the cricoid are type II; clefts with extension to the proximal 3 cm are type III; and a complete laryngotracheoesophageal cleft is type IV. Other classification schemes have been described and are available in the literature. The clefts of interest in this paper are Armitage type IA or Benjamin and Inglis

type I, ie, those with a defect located supraglottically extending down to, but not into, the cricoid cartilage. The interarytenoid area is thus deficient to the level of the true vocal cords.

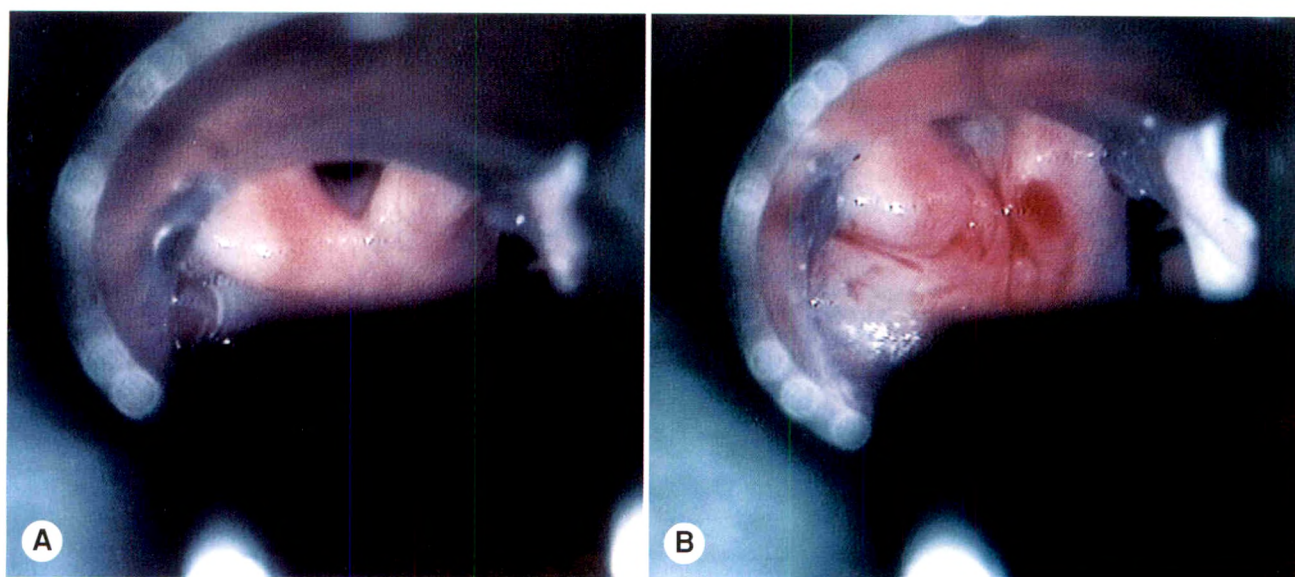
Many authors have advocated observation and expectant management of these clefts using positioning and thickened foods to prevent symptoms of choking and aspiration.^{4,5} Surgical repair by either an endoscopic or an external approach is advocated when the patient has symptomatic aspiration manifesting as cyanotic spells and recurrent lung infections. Patients with laryngeal clefts very often have associated airway abnormalities and other medical disorders that may compromise swallowing and laryngeal competency. The difficulty then lies in determining whether the laryngeal cleft is a significant contributor to the patients' symptoms and therefore should undergo repair.

We present a series of patients with symptoms and endoscopic findings consistent with supraglottic clefts. To determine the clinical significance of the cleft, we injected Gelfoam into the interarytenoid area at the time of diagnosis to serve as a temporizing measure and mimic an intact posterior glottic region.

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Endoscopic views. A) Type 1A posterior laryngeal cleft. B) After Gelfoam injection into interarytenoid area.

PATIENTS AND METHODS

Between March 1996 and December 1998, a series of 8 patients presented with signs and symptoms consistent with laryngeal incompetence that had not improved with medical therapy. All patients underwent a videofluoroscopic swallow study and endoscopic examination in the operating room. A combination of propofol (intravenously) and Sevoflurane (2% to 4% inhalational) was used to achieve an anesthetic plane with spontaneous respirations. Vocal cord mobility was assessed, and then the patient's anesthetic level was deepened. Esophagoscopy and rigid bronchoscopy were performed. Direct laryngoscopy with Venturi ventilation was performed, with especially close attention paid to the posterior glottic region. The interarytenoid region was splayed and assessed for a height difference between the level of the true vocal cords and the interarytenoid region. One gram of Gelfoam powder (Pharmacia & Upjohn, Kalamazoo, Mich) was mixed with approximately 4 mL of sterile normal saline solution to create an injectable consistency. This was loaded into a tuberculin syringe and injected submucosally through a 25-gauge spinal needle into the interarytenoid area. Approximately 1 mL was required to provide fullness to the deficient area. The patients were then followed up clinically, and some had repeat swallow studies.

CASE REPORT

A 6½-year-old boy with a history of agyria, cerebral palsy, and developmental delay presented with symptoms of choking and coughing with oral liquids or solids. He had had a gastrostomy tube placed at a young age for recurrent aspiration pneumonia.

Preoperative videofluoroscopic examination revealed oral motor deficits with decreased tone and strength of the oral musculature and lack of oral bolus control. He demonstrated frank aspiration with thin and thickened liquids, with no protective mechanism.

The findings on intraoperative examination were normal, except for a type 1A (supraglottic) laryngeal cleft (see Figure, A). Gelfoam was injected into the interarytenoid region to fill in the deficit (see Figure, B). On a follow-up swallow study, the patient still showed the oral-phase dysphagia present before the procedure, but he demonstrated an improvement in the pharyngeal phase, with no evidence of laryngeal penetration or aspiration. On the basis of these findings, he was allowed an oral diet and was noted to be markedly clinically improved, with no choking or coughing while eating.

RESULTS

Eight patients with signs and symptoms consistent with aspiration were evaluated by endoscopy and found to have posterior laryngeal abnormalities (see Table). Seven had interarytenoid clefts (type I or IA) and underwent injection of Gelfoam into the posterior region. One patient did not have an identifiable cleft, but had significantly abnormal splaying of the interarytenoid region. All 8 patients had abnormal outcomes on modified barium swallow studies, with 5 demonstrating aspiration. The most common presenting symptom was recurrent pneumonia and/or bronchitis. Choking and coughing spells during feeding occurred in half the patients, accompanied by cyanotic spells in 2 patients. Failure to thrive and a hoarse voice or cry were also noted.

Of great importance is the number of associated

PATIENT INFORMATION

Patient	Age	Signs and Symptoms	Barium Swallow Study	Associated Findings	Endoscopic Findings	Follow-up
1	6½ y	Coughing, choking with liquids, solids; recurrent aspiration	Oral motor deficits; aspiration with thin and thick liquids	Agyria, cerebral palsy; hypoplastic frontal lobes; seizure disorder; obstructive sleep apnea; gastrostomy tube	Interarytenoid cleft	Clinically greatly improved; no aspiration with any substance on repeat barium swallow study; oral diet
2	13 mo	Coughing, choking spells with feedings; cyanotic episodes	Transient laryngeal penetration with thin and thick liquids	Seizure felt to be associated with episode of aspiration; GERD	Interarytenoid cleft; hypermobile arytenoids	No choking spells with feedings for approximately 2.5 months; gradual return of symptoms; lost to follow-up
3	2½ y	Recurrent bronchitis, pneumonia; hoarse, low-pitched voice; reactive airway disease	Aspiration of thin liquids on multiple barium swallows	Williams' syndrome; reactive airway disease; GERD	Interarytenoid cleft; small defect in superior aspect of cricoid	No aspiration noted on repeat barium swallow study; allowed to take thin liquids
4	11 mo	Recurrent aspiration pneumonia	Significant silent aspiration before pharyngeal swallow; normal oral phase	Congenital herpes simplex II infection; prolonged ventilation for pneumonia at birth; maternal drug use	Splaying of interarytenoid region; no true cleft identified	Significant improvement clinically and on repeat barium swallow study; no aspiration with thin or thick liquids; trace laryngeal penetration
5	1½ y	Recurrent pneumonia; growth failure	Transient laryngeal penetration with thin liquids; no cough reflex	Undefined neurologic disorder; seizure disorder; stroke from hypercoagulability disorder; reactive airway disease; oral aversion; gastrostomy	Interarytenoid cleft; underwent Gelfoam injection twice	Clinically remarkably improved for 3 months; underwent second injection with resolution of symptoms; posterior cleft repair with auricular cartilage; no further pneumonia
6	5 mo	Coughing, choking with feedings; pneumonia; hoarse, cyanotic spells	Thin liquid penetration into larynx	Born at 37 weeks' gestation	Interarytenoid cleft; mild left main stem bronchus compression	Clinically improved; no coughing or choking; no pneumonia; intermittent laryngeal penetration but no aspiration on repeat barium swallow study
7	10 mo	Failure to thrive; recurrent bronchitis; congestion while eating	Pharyngeal-phase dysphagia; consistent laryngeal penetration and aspiration with thin and thick liquids	Failure to thrive; GERD; reactive airway disease	Interarytenoid cleft; mild laryngomalacia; trapped first tracheal ring	Clinically much improved for 3 months; considering cleft repair
8	3 y	Choking spells while eating; croupy cough	Aspiration with thin liquids; laryngeal penetration with pudding, solids; poor palatal elevation	Undefined mild neurologic disorder; mild developmental delay; GERD; failure to thrive	Interarytenoid cleft	No symptoms for 2 months; considering cleft repair

GERD — gastroesophageal reflux disease.

medical problems noted in these patients. Only 1 patient (No. 7) had no other significant problems. Five of the 8 patients had neurologic disorders, including agyria, congenital herpes simplex infection, Williams' syndrome (idiopathic hypercalcemia of infancy, associated with mental retardation), and 2 cases of undefined, clinically significant neurologic problems with developmental delay. Many of these patients had had a diagnosis of reactive airway disease

or recurrent croup before being evaluated for aspiration. Only 2 patients had other endoscopically diagnosed airway abnormalities: 1 with mild laryngomalacia and a possible trapped first tracheal ring, and the other with vascular compression of the left main stem bronchus.

All patients underwent Gelfoam injection into the deficient posterior glottic region. All patients demon-

strated clinical improvement after injection, with resolution of the symptoms and no further known admissions for sequelae of aspiration. The 4 patients with follow-up modified barium swallow studies showed improvement, with no evidence of aspiration. Four of the 8 patients had return of their symptoms. One has not returned for follow-up. One patient demonstrated such remarkable improvement after the injection that she underwent a second injection and subsequent repair of the cleft via an anterior laryngofissure approach. Two other patients' parents are considering definitive repair of the cleft, because of the improvement after injection. Four patients did not have return of symptoms at the time of last follow-up, and have not required further injections or surgical repair. This technique was initially considered as a temporary aid for the diagnosis of laryngeal incompetency, as Gelfoam is absorbable. Perhaps if followed further, some patients would be seen to have a return of symptoms; it may be that a delay in Gelfoam absorption occurred. It is also possible that some scarring resulted from the injection or a tissue response to the Gelfoam, accounting for a permanent effect.

DISCUSSION

The first report of a laryngeal cleft came from Richter in 1792.⁶ Laryngeal clefts have been considered rare congenital anomalies, but the recent literature has been documenting more cases, particularly the minor supraglottic clefts. The literature has repeatedly emphasized the elusive nature of the diagnosis of supraglottic clefts, and the need for a high index of suspicion in evaluating a patient with symptoms consistent with laryngeal incompetence. Parsons et al¹ reiterate the concept that type I and IA clefts have previously been underdiagnosed, with the symptoms attributed incorrectly to other anomalies or disease processes. Their series reports an incidence of type I posterior laryngeal clefts of 6.2%, whereas previously reported incidences ranged from 0.1% to 1.5%.

Differences of opinion regarding the appropriate management of type I and IA posterior laryngeal clefts exist in the literature. Glossop et al⁴ have stated that type I clefts require no surgical intervention, because they do not affect laryngeal competency. They reported only stridor as the presenting symptom. Recent literature, however, acknowledges the seriousness of laryngeal incompetence and the sequelae of aspiration that some of the type I and IA cleft patients suffer from.⁷⁻⁹ The options of endoscopic and open repair procedures are thoroughly discussed in the literature.⁷⁻¹⁰ The issue of which patients will benefit from repair is the emphasis of this article.

Patients with posterior laryngeal clefts are very often not otherwise healthy children. Parsons et al¹ report a 66% occurrence of other associated abnormalities in type I cleft patients, including 49% with endoscopic abnormalities and 24% with some form of developmental delay. Forty-four percent had gastroesophageal reflux disease, 5% had laryngomalacia, and tracheomalacia was the most common associated abnormality (15%).¹ Evans et al¹¹ report that 65% of their type I cleft patients have associated congenital anomalies. Mounghong and Holinger¹² report 7 of 11 patients to have significant cardiac and mediastinal anomalies. A Myer et al⁷ report of 10 patients with type I clefts documents multiple concurrent anomalies. Koltai et al⁹ report that 3 of 6 patients undergoing repair for primary supraglottic clefts had significant associated anomalies, including developmental delay. Our results in this small series agree with those reported in the literature, albeit with a higher incidence of concurrent neurologic abnormalities (63%) and a 25% occurrence of associated endoscopic abnormalities.

In these complicated cases, a "test dose" of Gelfoam was used to determine whether the posterior cleft was contributing significantly to the patients' symptoms of laryngeal incompetence, or whether other anomalies were responsible for their symptoms. All patients did show significant and sometimes remarkable improvement in their symptoms immediately after receiving the injection. The length of improvement in symptoms correlated well with the known length of Gelfoam persistence in situ (approximately 6 weeks).¹³ Follow-up modified barium swallow studies were performed in half the patients, with documentation of improvement in 3 of the 4 patients. More important, clinical improvement was noted by all parents, and hospital admissions for airway difficulties were eliminated. A similar case was reported by Nakahara et al,¹⁴ who used repeated collagen injections in what they called a type 1-a cleft. Three injections were performed over an 8-month time frame, with resolution of symptoms by age 30 months. No further reports of injections for diagnosis and/or treatment were found in the literature.

The injection was relatively easy to perform, with no need for special equipment, no significant lengthening of operating room time, no postoperative airway compromise, and no perceivable adverse effects. Also, no additional general anesthetic was required, as the injection was done at the time of diagnostic endoscopy. There were no identifiable complications related to the use of Gelfoam. One patient has since gone forward with posterior cleft repair on the basis of the consistent benefit noted from 2 injections. An-

other family is considering repair for their child.

CONCLUSION

As awareness and accurate diagnosis of type 1 and 1A posterior laryngeal clefts improves, more surgeons will be considering repair for those patients

whose clefts are causing significant difficulties with laryngeal incompetence. Injection of Gelfoam into the deficient posterior glottic region can relatively safely assist in determining which patients will benefit from repair and provide a temporary reprieve from symptoms associated with aspiration.

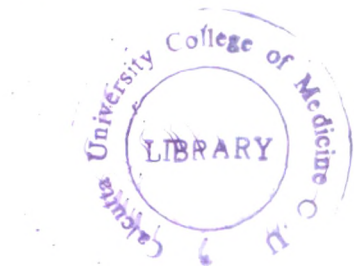
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PEDIATRIC FIBEROPTIC ENDOSCOPIC EVALUATION OF SWALLOWING

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Pediatric dysphagia is the presenting feature of many underlying diagnoses. Between July 1993 and July 1999, 643 fiberoptic endoscopic evaluations of swallowing (FEES) were performed on 568 patients. The median age of the population was 2.5 years (range, 3 days to 21 years). The principal medical and surgical diagnoses of the patients at the time of presentation to the FEES clinic were prospectively recorded: 36% of the patients presented with a diagnosis of structural abnormalities of the upper aerodigestive tract or airway; 26% with neurologic diagnoses; 12% with gastroenterological disorders; 8% with genetic syndromes; 7% with pulmonary dysfunction; 5% with prematurity; 3% with cardiovascular anomalies; and 2% with metabolic problems. The patients were classified according to the following feeding regimens: 9% normally fed; 38% orally fed with limitations; 13% orally fed, but with required supplemental tube feedings; and 40% prohibited from taking nutrition orally. The FEES enabled the following classification of feeding abnormalities: 15% had normal feeding; 56% exhibited behavioral abnormalities, including sensory-based feeding disorders; 15% exhibited structural abnormalities; 16% exhibited neurologic abnormalities; 1.5% exhibited metabolic abnormalities; and 0.5% exhibited cardiorespiratory abnormalities. The unique aspects of pediatric dysphagia are highlighted, and the role of FEES in the workup of this challenging aspect of pediatric otolaryngology is discussed.

KEY WORDS — dysphagia, fiberoptic endoscopy, swallowing.

INTRODUCTION

Endoscopic evaluation of swallowing for patients with dysphagia or aspiration was described first by Langmore et al¹ and soon after by Bastian.² The procedure involves 5 components: assessment of anatomy as it affects swallowing, evaluation of movement and sensation of critical structures within the hypopharynx and laryngopharynx, assessment of secretion management, direct assessment of swallowing function for food and liquid, and patient response to therapeutic maneuvers and interventions to improve the swallow.³ The patients for whom these authors developed this procedure were elderly, debilitated patients who, for the most part, had suffered cerebrovascular accidents that had produced their symptoms. The advantages of this form of testing, either video endoscopic evaluation of swallowing or fiberoptic endoscopic evaluation of swallowing (FEES), resulted from the ease of the testing process itself. The patient did not need to be moved from an intensive care setting to a fluoroscopy unit, nor did he or she need to swallow copious amounts of barium, which was either difficult to do or produced frank aspiration. In addition, the portability of the FEES procedure eliminated positional considerations that often caused problems in the radiology suite. Although the endoscopic evaluation did not provide a

view of the oral or esophageal phase of swallowing, it did provide an excellent view of the hypopharynx and larynx during the act of a swallow and allowed for a comparison among different food textures to identify which textures were more readily tolerated without aspiration. Appropriate postural adaptations or swallowing maneuvers that were effective in improving the safety and efficiency of swallowing were introduced as problems were detected, enabling the examiner to make appropriate interventional recommendations. Aviv et al⁴ coupled FEES with sensory testing of the larynx and hypopharynx region by introducing an air pulse to the region and documenting either a positive psychophysical response or a laryngeal adductor reflex. Aviv et al⁵ went on to show a correlation between the degree of laryngopharyngeal sensory discrimination deficit and aspiration.

The data from the adult FEES testing speak to the issue of aspiration in the context of attempting to prevent aspiration pneumonia. Neurologic disorders predominate, ranging from 67% to 71%.^{1,5} The issue of primary laryngeal disease manifesting itself as dysphagia and/or aspiration does occur in the adult population (in partial laryngectomy or partial laryngopharyngectomy patients, patients with unilateral vocal cord paralysis, etc), but these represent the minority of patients who present to an adult FEES clinic.

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TABLE 1. PATIENT AGES (N = 568)

Age (y)	No. of Patients
0-2.49	264
2.5-4.9	124
5.0-7.49	74
7.5-9.9	24
>10	82

The following is a description of the patient population seen at the FEES clinic at the Children's Hospital of Cincinnati. The purpose is to describe the various disorders associated with pediatric dysphagia. All patients were evaluated by FEES. The technique used is similar to that described by Aviv et al⁴ and will not be elaborated on here; particular aspects of the FEES protocol as it relates to the unique pediatric population will be discussed.

PATIENTS

From July 1993 to July 1999, 568 children underwent 643 FEES procedures for evaluation of dysphagia and/or possible aspiration. The ages of the children ranged from 2 months to 17 years (median, 2.5 years; Table 1). The children were referred either by the primary pediatrician or by a gastroenterologist, a speech pathologist, or an otolaryngologist. The patients arrived in the clinic with a presumed diagnosis for which the FEES was to be used to provide additional information and/or confirmation.

METHODS

A written explanation of the FEES procedure is sent in the form of a letter to the parents or caretakers before the clinic visit. The procedure is explained in simple terms, and the parent or caretaker is asked to bring the child's usual formula, foods, bottle and nipple, and utensils as appropriate.

A baseline screening of oral motor skills for feeding is completed by the speech pathologist before the FEES examination. The child is then brought into the room and either sits on the parent's or caretaker's lap or is accompanied by him or her, depending on the age of the child. The procedure is again explained to the parent or caretaker and the child if he or she is old enough. The patient's nasal passages are prepared with a 1:1 mixture of oxymetazoline hydrochloride and pontocaine several minutes before introduction of the flexible fiberoptic telescope. The parent or caretaker and the nurse assist in stabilizing the patient while the telescope is introduced via the nares to the point at which the larynx and hypopharynx regions are visualized. Any abnormalities in anatomy are noted. Other abnormalities, such as the presence of excessive secretions and penetration, aspiration, or efforts to clear accumulated secretions (swallow ini-

TABLE 2. PRESENTING DIAGNOSES (N = 568)

Diagnostic Category	% of Patients
Structural	35
Neurologic	33
Pulmonary	6
Genetic	7
Gastrointestinal	10
Cardiovascular	3
Metabolic	1
Prematurity	4
Psychiatric	1

tiation, throat clearing, coughing), are documented. The occurrence of spontaneous swallows overall is noted. Via the side port of the flexible telescope, air pulsations ranging from 2 to 10 mm Hg are administered to the aryepiglottic fold region, and the larynx and hypopharynx are observed for the laryngeal adductor reflex. An assessment of the presence of sensation of the laryngopharynx is possible even in the uncooperative child by means of this reflex. Once this evaluation is complete, the child is then given liquids and food textures as developmentally appropriate, and any premature spillage, laryngeal penetration, aspiration, or residue is noted. Children who are wholly uncooperative receive somatosensory testing alone, and feeding is not forced. The majority of children are able to be safely fed developmentally appropriate material with the assistance of the speech-swallow pathologist. Food coloring is added to all liquid and food material to allow for better visualization of swallowing parameters. Compensatory strategies, similar to those used during a videofluoroscopic swallowing study, may be introduced to improve the safety and efficiency of the swallowing process. Common strategies include positional alterations to provide optimal postural support to facilitate swallowing, altering the rate of liquid flow, increasing the viscosity of liquid, texture variations, nipple and bottle changes, and instructions to the primary feeder regarding modifications of feeding technique.

After thorough assessment, recommendations are made regarding the functional status of the patient in terms of different feeding paradigms.

RESULTS

Table 2 shows the most common diagnoses of children presenting to the FEES clinic. Table 3 shows a division of the patients into the following functional categories according to their current feeding problem: structural, neurologic, cardiorespiratory, metabolic, and behavioral feeding disorders (a model of classification described by Burklow et al⁶). The behavioral category represents a broad class of patients who exhibit disordered sensory processing with be-

TABLE 3. DIAGNOSES IN BURKLOW ET AL⁶ SYSTEM

<i>Diagnostic Category</i>	<i>% of Patients</i>
Behavioral	55
Neurologic	16
Structural	14
Cardiorespiratory	11
Metabolic	3
Normal	1

havioral manifestations of significant oral aversion and resistance to oral feeding, patients with conditioned dysphagia, or patients with abnormal sensory perception coupled with poor oromotor control and associated behavioral issues. Children with abnormal sensory perception and no behavioral issues are classified as having a neurologic problem. Table 4 gives a summary of the recommendations made for the patients seen at the FEES clinic.

DISCUSSION

To date, this series of 568 children who have undergone FEES for dysphagia and/or swallowing is the largest in the literature. This study is an extension of the first paper published on the subject of pediatric FEES in 1995.⁷ The purpose of this paper is not to evaluate the benefit of FEES as compared to a modified barium swallow study. Rather, we aim to highlight the variable diagnoses contributing to dysphagia in children and the role of FEES in the evaluation process.

The first point of comparison between adult FEES and pediatric FEES is that the process of using a fiberoptic flexible telescope in a child is time-intensive and requires assistance in order to stabilize the infant or child and prevent him or her from pulling out the telescope. Moreover, traversing the infant or child's nasal passages to visualize the larynx and hypopharynx is frequently more difficult than in the adult population because of the smaller size of the passages.

Once the pediatric larynx and hypopharynx are visualized, a thorough knowledge of normal pediatric anatomy is essential for determining what may be abnormal. Knowledge of normal and abnormal velopharyngeal and laryngopharyngeal anatomy, as well as a thorough understanding of the developmental changes that occur in the swallowing process as the child matures, is key to successful implementation of FEES in pediatric patients. The child's ability to cooperate may well be limited; therefore, it is not uncommon to have only sporadic glimpses of the anatomy between cries. The position of the cricoid cartilage in the child initially approximates the fourth cervical vertebra; it descends to its final position at

TABLE 4. BASELINE FEEDING RECOMMENDATIONS

<i>Feeding Category</i>	<i>% of Patients</i>
No oral feeding	40
Oral feeding with some restrictions	38
Oral feeding with tube feed supplements	13
Normal feeding	9

the level of the sixth to seventh cervical vertebrae by 15 years of age.⁸ The size of the larynx also varies with age, beginning with a subglottic diameter of 4 mm or greater and then increasing over time. Finally, the relative proportion of the arytenoids to the vocal cords is greater in the child and diminishes as the child grows and the vocal cords lengthen.

The number of diagnoses made possible by flexible fiberoptic telescopic examination for the children who underwent FEES was exceedingly high. If we were to include only those findings that are most obviously seen on fiberoptic examination, namely, laryngomalacia, vocal cord paralysis, and findings suggestive of gastroesophageal reflux, the incidence approximates 11%. When other diagnoses, such as laryngeal clefts, that may be suspected from the examination are included, the incidence rises to 17.5%. It may be argued these diagnoses can be made by flexible fiberoptic endoscopy alone and that such endoscopy combined with a modified barium swallow study provides adequate information. The purpose of this paper is not to argue that FEES should replace modified barium swallow evaluations. Rather, FEES is designed to be complementary to the current armamentarium of diagnostic procedures. It is a relatively easy test that stems naturally from a procedure that pediatric otolaryngologists are well versed in and would perform on the majority of these children to assess the airway even if it was not to assess swallowing. Adding the swallowing evaluation to the fiberoptic endoscopy can reveal useful initial, interval, or adjunct information regarding swallowing function, can have implications regarding surgical laryngeal reconstructive procedures and the effect on swallowing function, and can provide a further clarification of findings of previous instrumental examinations, such as videofluoroscopy. An example would be to shed light on a child who appears to have laryngeal penetration on modified barium swallow testing (especially when the lateral films only are viewed) but on FEES shows contact of liquid or food on the pharyngeal surface of the aryepiglottic fold, rather than on the endolaryngeal surface. The panoramic view of FEES allows more accurate identification of the location and degree of laryngeal penetration overall. In some cases, anatomic conditions may bring the epiglottis into contact with the tongue base. As the patient swallows, material will come into con-

tact with the laryngeal surface of the epiglottis as a consequence of anatomy rather than of swallowing abnormality. This contact will be interpreted as laryngeal penetration with implications regarding the safety of swallowing during fluoroscopy, but this same finding as seen during endoscopic swallowing evaluation can be interpreted in the context of anatomy. However, in order to draw any rational conclusions from FEES, it is essential to know whether the visualized anatomy is normal or not.

In this study, 19% of patients presented with an initial diagnosis of subglottic stenosis. This incidence is reflective of the particular patient population seen at the Children's Hospital Medical Center in Cincinnati and the high volume of laryngotracheal reconstructive procedures that are performed in this institution. Currently, those children undergoing laryngotracheal reconstruction with any suggestion of feeding difficulty or possible aspiration undergo FEES to see whether opening the airway would worsen the situation with reference to possible aspiration. The majority of laryngotracheal reconstructive candidates are undergoing FEES. The initial results of this testing have been reported⁹; more work remains to be done to establish which patients would benefit from preoperative FEES.

Dysphagia in an adult is often the direct result of an inciting event, ie, a cerebrovascular accident. In

contrast, dysphagia in the pediatric population may also have had an inciting event, but that inciting event may well have been treated some time ago or may have resolved with the dysphagia remaining. This may be in part due to the timing of the inciting event with reference to the critical period of development in which the child is learning the complex task of swallowing.¹⁰ A child presenting to the FEES clinic with a diagnosis of dysphagia may well represent a complex picture in which an inciting event or several inciting events have been coupled with a behavioral response that manifests as dysphagia. It is in this situation that a team of specialists including an otolaryngologist and a speech pathologist is needed to fully evaluate the problem.

CONCLUSION

Pediatric FEES is a relatively new diagnostic method to add to and complement the current armamentarium of techniques for evaluating dysphagia and/or aspiration. It provides the ability to diagnose many of the laryngeal disorders that may affect the child, while at the same time evaluating the swallowing mechanism itself. When used by a pediatric otolaryngologist trained in the subtleties of the pediatric airway anatomy, it can provide meaningful information that can have an impact on clinical decision-making.

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LARYNGOPHARYNGEAL SENSORY DEFICITS IN PATIENTS WITH LARYNGOPHARYNGEAL REFLUX AND DYSPHAGIA

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There are no reliable means of quantifying the edema that results from acid exposure to the posterior larynx in patients with laryngopharyngeal reflux (LPR). However, it is possible to quantify laryngopharyngeal sensitivity in these patients by endoscopic administration of air pulses to the laryngeal mucosa in order to elicit the laryngeal adductor reflex. The purpose of this study was to determine whether patients with LPR have sensory deficits in the laryngopharynx, and whether treatment of these patients with a proton pump inhibitor (PPI) results in resolution of sensory deficits. Flexible endoscopic evaluation of swallowing with sensory testing was prospectively performed in 54 patients with dysphagia without neurologic disease and in 25 healthy controls. The laryngopharyngeal sensory level, posterior laryngeal edema, and LPR were assessed. We defined LPR as passage of food material from the esophageal inlet retrograde into the hypopharynx. Patients with LPR were placed on 3 months of omeprazole or lansoprazole and then retested. Patients without LPR were placed on H₂ blockers for 3 months and then retested. In the dysphagia group, 48 of 54 patients (89%) had edema of the posterior larynx, and 42 of 54 (78%) had laryngopharyngeal sensory deficits. We noted LPR in 38 of 54 (70%). In the control group, 1 of 25 subjects (4%) had edema, sensory deficits, and LPR. The differences in incidence of edema, sensory deficits, and LPR between the dysphagia group and the control group were significant ($p < .001$, χ^2 test). Twenty-three patients with LPR placed on a PPI returned for follow-up, with improvement in laryngeal edema in 14 of the 21 (67%) who had pretreatment edema and resolution of sensory deficits in 15 of the 19 (79%) who had pretreatment deficits. In the non-LPR, non-PPI group, 11 of 16 patients returned for follow-up, with improvement in laryngeal edema in none of the 11 and improvement in sensory deficits in 1 of the 11 (9.1%). The differences in improvement in laryngeal edema and sensory deficits between the LPR, PPI group, and the non-LPR, non-PPI group were significant ($p < .01$, Fisher's exact test). We conclude that patients with dysphagia and edema of the posterior larynx as a result of LPR have sensory deficits in the laryngopharynx. Treatment of these patients with a PPI appears to result in resolution of laryngopharyngeal edema and improvement of sensory deficits, both subjectively and objectively.

KEY WORDS — dysphagia, endoscopy, reflux, sensation.

INTRODUCTION

Reflux of acid into the hypopharynx, or laryngopharyngeal reflux (LPR), is a very common and potentially debilitating chronic disease process.¹ The symptoms of LPR typically include hoarseness, dysphagia, globus sensation, chronic cough, and frequent throat clearing.²⁻⁴ Heartburn and regurgitation, the classic symptoms of gastroesophageal reflux disease, are unusual symptoms in patients with LPR.^{3,5-7} The physical examination findings of LPR may include edema of the arytenoids, aryepiglottic folds, and interarytenoid regions; erythema of the larynx; vocal fold granuloma; and laryngeal ulcer, erosion, or exudate.^{3,5,6,8} Edema of the larynx, not erythema, is thought to be the clinical hallmark of LPR.^{1,2,5,9}

Traditionally, the diagnosis of LPR is made by a combination of history-taking, physical examination, and diagnostic instrumentation testing. Currently, double-probe 24-hour pH monitoring is considered to be the most sensitive and specific method of mak-

ing a diagnosis of LPR.^{2,3,6,7} However, patients may not want to have any type of foreign body in the nose and laryngopharynx for 24 hours in order to be treated for their complaints.

Over the past decade, endoscopic evaluation of swallowing has emerged as a less expensive, nonradiologic alternative to a modified barium swallow study for the diagnosis and management of patients with dysphagia.^{10,11} One of the distinct advantages of endoscopic evaluation of swallowing relative to videofluoroscopy is the ability to clearly observe topographic changes in both laryngopharyngeal mucosal thickness and color. In addition, it has been noted that LPR can be readily detected during endoscopic swallowing evaluations.¹² Flexible endoscopic evaluation of swallowing with sensory testing (FEESST), a quantitative method of evaluating laryngopharyngeal sensitivity during an endoscopic swallowing evaluation, may be useful not only in documenting LPR, but also in quantifying the arytenoid edema

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often noted during endoscopic examinations of the larynx in patients with LPR.^{9,13} In this study, laryngopharyngeal sensation was determined by endoscopically delivering discrete pulses of air to the laryngopharyngeal mucosa, at various pressure intensities, in order to elicit the laryngeal adductor reflex (LAR), a brain stem-mediated airway protective reflex.^{14,15}

The advent of the proton pump inhibitor (PPI) has revolutionized the management of patients with LPR.¹⁶⁻¹⁸ However, short of frequently repeating 24-hour pH probe testing on patients treated with PPIs, the consequences of PPI therapy are primarily judged subjectively by repeat history-taking and follow-up physical examinations. This study, therefore, had two purposes: 1) to determine whether patients with historical and clinical evidence of LPR have sensory deficits in the laryngopharynx and 2) to quantify the consequences of PPI therapy.

MATERIALS AND METHODS

Fifty-four patients with dysphagia and 25 healthy control subjects without dysphagia were prospectively evaluated over an 18-month period. Dysphagia was defined as any subjective or objective difficulty handling food or secretions, or coughing or choking during ingestion of solid or liquid food. None of the test subjects or controls were cigarette smokers. The patients and controls did not have a history of stroke or chronic neurologic disease. In addition, neither the patients nor the controls had complaints of postnasal drip, facial pain or pressure, or purulent rhinorrhea. Both patients and controls were ambulatory outpatients without a history of vocal fold paralysis or tracheostomy who had not used a PPI or an H₂ receptor antagonist (H₂ RA) for at least 6 months before the study.

The patient group were patients consecutively seen with a complaint of dysphagia who satisfied the aforementioned criteria. Because the patient group's primary complaint was dysphagia, this patient population was extremely eager to have a comprehensive evaluation that might even hint at the cause of their complaint. Therefore, all patients agreed to have at least an initial FEESST examination.

A detailed history was obtained from each individual in the study, focusing on the presence or absence of the following symptoms: dysphagia or globus sensation, throat clearing, heartburn or indigestion, increased phlegm, and cough.

Fifteen minutes before the flexible laryngoscopy portion of the FEESST, each subject, patients and controls, was given 30 mL of apple juice that had 1 mL of green food coloring mixed in. All subjects sub-

sequently underwent a FEESST. The FEESST protocol has been described in detail previously.¹² Initially, an endoscopic examination of the larynx was performed. Attention was specifically directed toward the presence or absence of the following findings: 1) interarytenoid edema, 2) arytenoid edema, 3) arytenoid erythema, and 4) vocal fold edema. Interarytenoid edema was defined as edema either obliterating the concavity of the posterior glottic wall or creating a convexity or obstruction of the posterior glottic wall. Arytenoid edema was defined as obliteration of the mucosal protuberance of the cuneiform and corniculate cartilages, as well as thickening of the mucosa at the site at which the aryepiglottic fold joins the arytenoid. Arytenoid erythema was defined as redness of the arytenoid mucosa relative to the surrounding laryngopharyngeal mucosa. Vocal fold edema was defined as loss of vocal fold sharpness and/or polypoid changes of the vocal fold mucosa.

Subsequent to the flexible laryngoscopy, laryngopharyngeal sensory discrimination testing was carried out by endoscopically delivering 50-ms pulses of air to the mucosa just anterior to the arytenoid while varying the pressure intensity of the air pulse in order to elicit the LAR. The LAR is identified by direct visualization of vocal fold adduction on a video monitor receiving a real-time image from the fiberoptic telescope. When the reflex is absent, the vocal folds fail to close after stimulation in this region. The type of vocal fold closure taking place in response to air pulse stimulation was a brief, rapid, nonrhythmic vocal fold adduction clearly distinguishable from the rhythmic vocal fold movement seen during normal respiration. The mean of the 2 lowest pressures from repeated air pulse stimulations that elicited brief laryngeal adduction was recorded as that subject's threshold.

The air pulse pressure ranged from 2 to 10 mm Hg and was delivered from an air pulse stimulator and endoscope made especially for this purpose (Pentax Precision Instrument Corp, Orangeburg, NY). In all phases of this study, the same endoscope was used to perform the laryngopharyngeal endoscopic examination, sensory testing, and swallowing evaluation. Further, in all cases, the same halogen light source was used to provide illumination to the endoscope (LH-150, Pentax). As described in earlier work, laryngopharyngeal sensory discrimination thresholds were defined as normal (<4.0 mm Hg air pulse pressure), moderately impaired (4.0 to 6.0 mm Hg air pulse pressure), or severely impaired (>6.0 mm Hg air pulse pressure). In all cases, if subjects did not respond to a 50-ms air pulse at >6.0 mm Hg, a continuous air pulse of 1 second was administered to determine whether the LAR could be elicited.^{14,15}

TABLE 1. INITIAL LARYNGEAL EXAMINATION FINDINGS

Finding	Dysphagia Group (n = 54)		Controls (n = 25)	
	No.	%	No.	%
Interarytenoid edema	47	87*	1	4
Arytenoid edema	48	89*	1	4
Arytenoid erythema	16	30	0	0
Vocal fold edema	7	13	1	4

*p < .001, compared to control group.

After the sensory testing procedure was performed, various solid and liquid food consistencies were given to the patients and controls, with all subjects receiving at least a pureed consistency and a thin liquid consistency. Five swallowing parameters were examined in detail: 1) spillage, defined as the head of the food bolus's entering the hypopharynx more than 1 second before the swallowing response occurred; 2) pharyngeal residue or pooling, defined as persistence of green food material along the pharyngeal walls or within the pyriform sinuses or valleculae; 3) laryngeal penetration, defined as passage of material into the larynx but not below the vocal folds; 4) aspiration, defined as passage of material below the level of the true vocal folds into the trachea; and 5) reflux, defined as passage of material from the esophageal inlet retrograde into the laryngopharynx before, during, or after the swallow. All examinations were recorded on videotape.

All patients with dysphagia who were noted to be having reflux during the FEESST were subsequently placed on an antireflux regimen that included dietary and positional changes (reflux precautions). In addition, patients — on alternating weeks of the study — were given a 3-month course of either omeprazole 20 mg twice a day or lansoprazole 30 mg once a day. Patients with no reflux during the FEESST were placed on reflux precautions and H₂ RA therapy, either ranitidine 150 mg once a day or famotidine 20 mg once a day.

The patients were restudied according to protocol approximately 90 days after the initial FEESST. On repeat FEESST testing, particular attention was directed toward patient symptoms, laryngoscopic findings, and sensory testing results.

STATISTICAL ANALYSIS

The association between LPR and the presence of laryngopharyngeal sensory deficits and the associations between laryngopharyngeal sensory deficits and laryngeal penetration and aspiration were analyzed with χ^2 tests (with a continuity correction) and quantified by a risk ratio. McNemar's test was used to

TABLE 2. FEESST FINDINGS OF ENTIRE DYSPHAGIA COHORT AND CONTROLS

FEESST Finding	Dysphagia Group (n = 54)		Controls (n = 25)	
	No.	%	No.	%
Reflux	38	70	0	0
Sensory deficits	42	78*	1	4

*p < .001, compared to control group.

test for differences according to PPI treatment (before versus after) in the proportion of patients with penetration and in the proportion with aspiration. Fisher's exact test was used to assess the statistical significance of differences in the rates of improvement for both edema and laryngopharyngeal sensory deficits between patients treated with PPIs and patients not treated with PPIs. All tests were 2-sided and performed at the .05 level.

RESULTS

Control Group. The control group consisted of 7 women and 18 men with an age range of 26 to 70 years and a mean age of 39 years (SD = 10). Although a vigorous attempt was made to age-match the control group to the dysphagia group, we were unable to find age-matched controls who were nonsmokers without rhinitis or sinusitis complaints who were not taking PPIs or H₂ RAs. None of the control group reported any LPR symptoms. On physical examination, 1 of the 25 controls (4.0%) had interarytenoid and arytenoid edema, and 1 of the 25 (4.0%) had edema of the vocal folds (Table 1). The FEESST findings revealed that 1 of the 25 (4.0%) had bilateral moderate laryngopharyngeal sensory deficits — the same patient who had arytenoid and interarytenoid edema. The LAR was elicited in all subjects. None of the control subjects demonstrated severe sensory deficits (as defined in the Materials and Methods section), reflux, laryngeal penetration, or aspiration during the FEESST (Table 2).

Initial FEESST of Dysphagia Group. Fifty-four patients with dysphagia presented for the initial FEESST. There were 22 women and 32 men with an age range of 24 to 97 years and a mean age of 68 years (SD = 17). The most common symptoms, in addition to dysphagia and globus sensation, were chronic cough and frequent throat clearing (Table 3).

Physical examination findings revealed either arytenoid edema or interarytenoid edema in 52 of the 54 patients (96%; Table 1). The difference from the control group was significant ($\chi^2 = 48.7$, $p < .001$). Laryngopharyngeal sensory deficits were seen in 44 of the 52 patients (85%) with edema of the posterior larynx (Table 2). The difference from the control

TABLE 3. PRESENTING SYMPTOMS OF ENTIRE DYSPHAGIA COHORT

Symptom	Dysphagia Group (n = 54)	
	No.	%
Dysphagia	54	100
Cough	34	63
Throat clearing	27	50
Phlegm	17	31
Heartburn	5	9

group was significant ($\chi^2 = 36.6$, $p < .001$; Tables 1 and 2). The LAR was elicited in all patients.

The initial FEESST group was further divided into a reflux cohort and a nonreflux cohort. Thirty-eight of the 54 patients (70%) had reflux during the FEESST. This difference from the incidence of reflux in the control group was significant ($\chi^2 = 17.7$, $p < .001$). Of the 38 patients with reflux, 3 refused PPI therapy and were excluded from further study, thus leaving 35 patients who were treated with a PPI. Of these 35 patients, arytenoid edema was seen in 30 (86%), and a sensory deficit was seen in 27 (77%; Table 4).

Looking more closely at the 35 patients with reflux, we noted the following: 18 of the 35 had severe sensory deficits, and 17 had either no deficits ($n = 8$) or moderate deficits ($n = 9$). Of the 18 patients with severe sensory deficits, 16 (89%) had penetration on the swallowing evaluation portion of the FEESST, and 9 (50%) had aspiration. Of the 17 patients with no deficits or moderate deficits, 3 (18%) demonstrated penetration, and 2 (12%) demonstrated aspiration (Table 5). There was a significant difference in the incidence of penetration between those with severe sensory deficits and those with no deficits or moderate deficits ($p = .001$; risk ratio, 5.03; 95% confidence interval [CI], 1.781 to 14.248). The difference in incidence of aspiration between those with severe sensory deficits and those with no deficits or moderate deficits was also significant ($p = .038$; risk ratio, 4.25;

TABLE 4. CHARACTERISTICS OF REFLUX AND NONREFLUX COHORTS ON INITIAL FEESST

Finding	Reflux* (n = 35)		No Reflux (n = 16)	
	No.	%	No.	%
Interarytenoid edema	29	83	15	94
Arytenoid edema	30	86	15	94
Arytenoid erythema	11	31	4	25
Vocal fold edema	5	14	2	13
No sensory deficits	8	23	2	13
Moderate sensory deficits	9	26	1	6
Severe sensory deficits	18	51	13	81

FEESST — flexible endoscopic evaluation of swallowing with sensory testing.

*Reflux patients who were placed on proton pump inhibitors.

TABLE 5. INITIAL FEESST RESULTS IN REFLUX COHORT (N = 35)

FEESST Finding	Laryngopharyngeal Sensory Deficit					
	No Deficit (n = 8)		Moderate Deficit (n = 9)		Severe Deficit (n = 18)	
	No.	%	No.	%	No.	%
Laryngeal penetration	0	0	3	33	16	89
Aspiration	0	0	2	22	9	50

95% CI, 1.068 to 16.916).

The initial FEESST findings of the 23 patients who returned for follow-up showed that 19 of the 23 (83%) had either a bilateral severe or a bilateral moderate sensory deficit. Seven of the 23 (30%) displayed aspiration (6 with bilateral severe sensory deficits and 1 with bilateral moderate sensory deficits), and 11 (48%) displayed laryngeal penetration (8 with bilateral severe sensory deficits and 3 with bilateral moderate sensory deficits).

The nonreflux, non-PPI cohort consisted of 16 patients. Of these, 15 (94%) had both arytenoid and interarytenoid edema, as well as sensory deficits. The FEESST results in this group showed aspiration in 2 of the 16 (13%) and laryngeal penetration in 12 (75%); all patients with aspiration and laryngeal penetration had bilateral severe sensory deficits. The initial physical examination and FEESST findings in the 11 non-reflux patients who returned for follow-up demonstrated that all 11 had posterior laryngeal edema and that 10 (91%) had sensory deficits. At the time of the follow-up examination, 8 of these 11 patients had laryngeal penetration, and 1 had aspiration.

Follow-up FEESST of Dysphagia Group. Twenty-three patients in this cohort presented for a follow-up FEESST after a 3-month course of either omeprazole or lansoprazole. The patients reported resolution of nearly all of their phlegm and throat clearing complaints. The dysphagia symptoms improved in 17 of the 23 (74%), and cough improved in 11 of 15 (73%) in comparison to their pretreatment symptoms (Table 6). Of the 21 patients who had pretreatment posterior laryngeal edema, 14 (67%) showed subjective improvement after PPI therapy (Table 6). Further, of the 19 patients who had pretreatment sensory deficits, repeat FEESST testing performed after PPI therapy revealed improvement in sensory deficit, either from a severe deficit to moderate or normal, or from a moderate deficit to normal in 15 patients (79%; Table 6). Overall, on follow-up sensory testing, only 5 of the 23 patients (22%) had sensory deficits.

The findings on the endoscopic swallowing evaluation portion of the FEESST in the 23 patients who

TABLE 6. FOLLOW-UP FEESST RESULTS IN PPI-TREATED GROUP (N = 23)

Finding	Pre-PPI		Post-PPI	
	No.	%	No.	%
Dysphagia	23	100	6	26
Cough	15	65	4/15	27
Throat clearing	13	56	1/13	7.7
Phlegm	9	39	0	0
Heartburn	3	13	0	0
Interarytenoid edema	21	91	7/21	33
Arytenoid edema	21	91	6/21	29
Arytenoid erythema	7	30	2/7	29
Vocal fold edema	2	8.7	0	0
No sensory deficits	4	17	18	78
Moderate sensory deficits	7	26	2	8.7
Severe sensory deficits	12	52	3	13

PPI — proton pump inhibitor.

returned for follow-up after PPI treatment were as follows: 3 (13%) had laryngeal penetration, and 1 (4.3%) had aspiration. In a comparison to the pre-treatment group, the decreased incidence of laryngeal penetration after PPI treatment was significant ($p = .005$, McNemar's test). In addition, in a comparison to the pre-PPI therapy group, the decreased incidence of aspiration after PPI treatment was also significant ($p = .014$, McNemar's test). Moderate or severe laryngopharyngeal sensory deficits were only seen in this subgroup of patients with penetration or aspiration. Representative endoscopic images of the laryngopharynx made before and after PPI treatment are shown in the Figure.

Of the nonreflux, non-PPI cohort of 16 patients, 11 patients presented for a follow-up FEESST. All

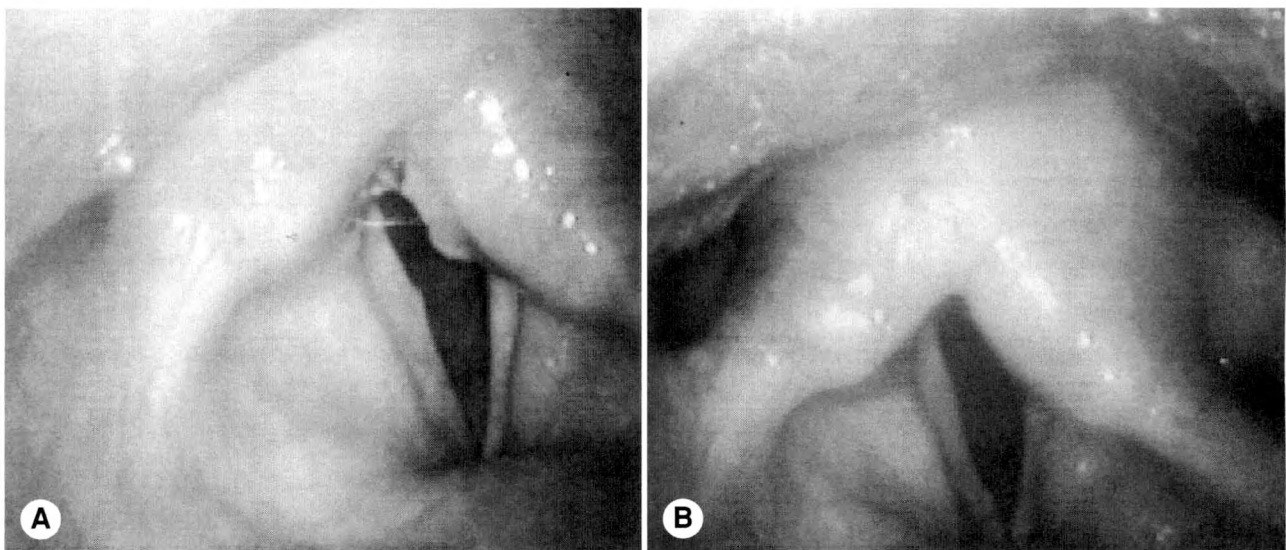
TABLE 7. FOLLOW-UP FEESST RESULTS IN H₂ BLOCKER-TREATED GROUP (N = 11)

Finding	Pre-H ₂ Blocker		Post-H ₂ Blocker	
	No.	%	No.	%
Dysphagia	11	100	11	100
Cough	4	36	3	27
Throat clearing	6	55	5	45
Phlegm	1	9.1	1	9.1
Heartburn	0	0	0	0
Interarytenoid edema	11	100	11	100
Arytenoid edema	11	100	11	100
Arytenoid erythema	3	27	2	18
Vocal fold edema	0	0	0	0
No sensory deficits	1	9.1	1	9.1
Moderate sensory deficits	0	0	1	9.1
Severe sensory deficits	10	91	9	82

11 patients had persistent symptoms and posterior laryngeal edema. Ten of the 11 had persistent laryngopharyngeal sensory deficits on repeat FEESST testing (Table 7). In a comparison of the PPI-treated group to the non-PPI-treated group, the improvement in posterior laryngeal edema in the PPI-treated cohort was significant ($p < .01$, Fisher's exact test), and the resolution of sensory deficits was also significant ($p < .01$, Fisher's exact test).

DISCUSSION

The predominant physical examination finding of posterior laryngeal edema, rather than erythema, in this cohort of dysphagia patients corroborates previous work suggesting that edema of the larynx is the hallmark of LPR.^{2,9} This study establishes that the



Endoscopic views of laryngopharynx of patient in study. A) At initial flexible endoscopic evaluation of swallowing with sensory testing, demonstrating left arytenoid granuloma and edema of arytenoids. B) Same patient, 3 months later, after 3-month course of proton pump inhibitor. Note resolution of left arytenoid granuloma and subjective resolution of arytenoid edema.

sensory deficits associated with posterior laryngeal edema can be objectively quantified. It also demonstrates that dysphagic patients with actual reflux during a FEESST have sensory deficits in the posterior larynx. This study also shows that one can begin to quantify the effects of PPI therapy in terms other than, "The laryngeal swelling perhaps appears to look somewhat better."

Interestingly, the historical complaints and physical examination findings suggestive of LPR appeared to be present whether or not actual reflux events were noted during the FEESST. Although endoscopic swallowing evaluations may readily detect reflux into the hypopharynx, a finding of no reflux at the time of a FEESST does not exclude the possibility that reflux can take place during another portion of the patient's day. Our results suggest that a healthy nonsmoker without rhinitis complaints who is complaining of dysphagia and frequent throat clearing, with findings of posterior laryngeal edema and severe laryngopharyngeal sensory deficits, likely is having reflux into the hypopharynx, and treatment with a PPI is justified. The proposal of treatment for reflux based on a series of historical and physical findings without documenting the reflux under direct vision or by 24-hour pH probe testing is not new.¹⁸ What we have added is an objective means of characterizing sensory deficits associated with the posterior laryngeal examination findings.

It appears that the anatomic and physiological changes that occur in the hypopharynx as a result of LPR contribute to significant abnormalities in the swallow. Patients with bilateral severe laryngopharyngeal sensory deficits had a risk of laryngeal penetration that was 5 times that of those with no sensory deficits or moderate sensory deficits, and a risk of aspiration that was more than 4 times that of patients with no deficits or moderate deficits. Furthermore, treatment of very symptomatic patients with a PPI, as opposed to an H2 blocker, not only significantly reduced posterior laryngeal swelling and the severity of sensory deficits, but also significantly reduced the number of untoward swallowing events such as

laryngeal penetration and aspiration.

One of the unintended findings of this study was the remarkable efficacy of PPI therapy as opposed to H2 RA therapy. Although the literature on gastroesophageal reflux disease is quite clear about the superior efficacy of PPIs as opposed to H2 RAs or placebo in treating that disease,¹⁹ there are no placebo-controlled studies comparing PPIs to H2 RAs for the treatment of LPR. Therefore, patients in this study who were not actually having reflux during the FEESST were placed on what was expected to be adequate therapy for their symptoms and findings. Clearly, well-controlled studies comparing different treatment methods for LPR are needed, and will be the subject of subsequent investigations.

Although the patient response to 3 months of treatment with a PPI resulted in significant improvement in symptoms and physical findings in this cohort, there was a subset of approximately 25% of patients who continued to have symptoms and persistent pathological physical examination findings. The gastroenterology literature and otolaryngology literature consistently report a subgroup of approximately 30% of patients who do not respond to typical courses of PPI therapy.^{16,18,20} Our findings in a select group of extremely symptomatic patients mirrors this previous experience. Future work will concentrate on symptom assessment, physical findings, and therapeutic methods in LPR patients without dysphagia complaints.

CONCLUSION

Edema of the posterior laryngeal mucosa in patients with dysphagia who have reflux during an endoscopic swallowing evaluation frequently results in laryngopharyngeal sensory deficits. Treatment of reflux patients with a PPI appears to objectively reduce the site-specific edema seen in these patients. Quantification of sensory deficits associated with posterior laryngeal edema can be applied as part of the complex decision-making process regarding implementation of particular treatment methods for patients with reflux disease.

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EIGHTH SYMPOSIUM ON COCHLEAR IMPLANTS IN CHILDREN

The Eighth Symposium on Cochlear Implants in Children will be held in Los Angeles, California, February 28 to March 3, 2001. For information, visit the web site www.hei.org/ci2001; telephone Caroline Sakai at (213) 353-7001; or write to House Ear Institute/CI2001, 2100 W Third St, Los Angeles, CA 90057.

FOREIGN BODY IN THE TRACHEA

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Tracheal foreign bodies in pediatric patients may result in significant morbidity and mortality. We present the case of a 6-year-old child who required a tracheotomy to secure her airway and remove the foreign body.

KEY WORDS — foreign body, trachea, tracheotomy.

A 6-year-old girl had a cyanotic coughing spell while eating a hamburger. She was taken to the emergency room by a rescue squad and, on further inquiry, admitted to placing a marble in her mouth before the acute event. On initial examination, she was tachypneic and using accessory muscles of respiration. She was maintaining oxygen saturation levels in the high nineties while lying in the left lateral decubitus position. On sitting up, she became more tachypneic, and the oxygen saturation level dropped to the mid-eighties. She was kept in the left lateral decubitus position with 2 L of oxygen during the remainder of the examination. On auscultation, a thump was heard throughout her chest with both inspiration and expiration. A chest radiograph demonstrated loss of the distal tracheal air column, but no evidence of a foreign body (Fig 1).

The patient was brought emergently to the operating room for bronchoscopy and removal of the foreign body. Induction of anesthesia was complicated by the inability to maintain the child's oxygen saturation level in any position other than the left lateral decubitus. Approximately 15 minutes was required to achieve an adequate plane of anesthesia to perform bronchoscopy. A 5.0-mm pediatric bronchoscope was placed, and a round metal-coated object was visualized below the true vocal cords. The foreign body moved distally and proximally with each ventilation. Multiple attempts to remove the foreign body were performed with a Fogarty catheter. However, the diameter of the object made its exit through the glottic inlet impossible. The decision was made to perform a tracheotomy to secure the airway and remove the foreign body.

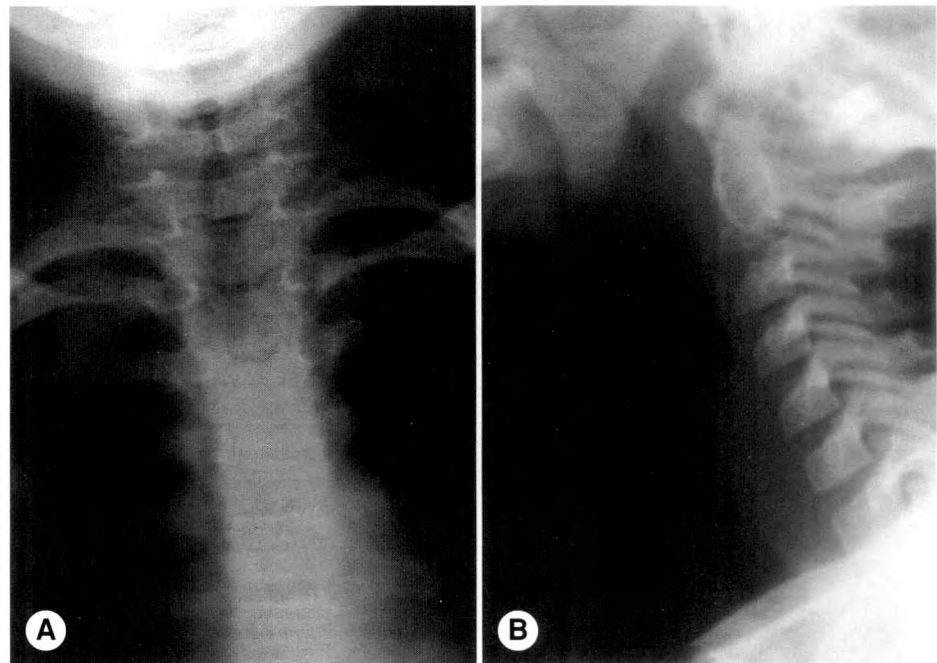


Fig 1. Chest radiographs demonstrate loss of distal tracheal air column. A) Frontal view. B) Lateral view.

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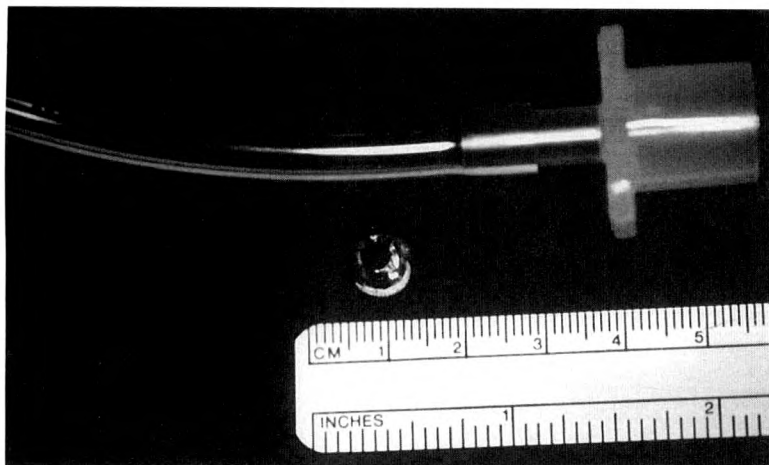


Fig 2. Foreign body, hair bead, and its relation in size to lumen of 5.5-mm endotracheal tube.

A tracheotomy was performed while the child was mask-ventilated. Oxygen saturation levels were maintained in the high nineties throughout the procedure. After the tracheotomy was completed, attention was focused on the foreign body. With a Fogarty catheter in the distal trachea and a 5.5-mm endotracheal tube inserted from above, the foreign body was isolated at the level of the stoma and removed with a hemostat. Figure 2 demonstrates the foreign body, a metal-coated hair bead, and its relation to the lumen of a 5.5-mm endotracheal tube. The tracheotomy tube was then replaced and the child returned to the recovery room in stable condition.

The child's postoperative course was unremarkable. Bronchoscopy performed 6 days after the foreign body removal yielded normal findings, and she was decannulated. Her stoma was well healed by her

1-month examination.

DISCUSSION

Pediatric tracheal foreign bodies result in high rates of morbidity and mortality. Generally, they can be extracted with a rigid bronchoscope and foreign body forceps. However, some foreign bodies are difficult to remove because of their shape and size. The endoscopist should be prepared to perform a tracheotomy to secure the airway and remove the foreign body. Performing an open procedure should not be viewed as a failure of the surgeon as an endoscopist. Many cases of tracheotomy to remove airway foreign bodies have been reported in the literature by highly skilled surgeons, and the decision to abandon an endoscopic approach during a procedure is more safely made before the patient's status is critical.¹

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OPTIMIZED SPEECH UNDERSTANDING WITH THE CONTINUOUS INTERLEAVED SAMPLING SPEECH CODING STRATEGY IN PATIENTS WITH COCHLEAR IMPLANTS: EFFECT OF VARIATIONS IN STIMULATION RATE AND NUMBER OF CHANNELS

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The purpose of this study was to investigate the effect of systematic variations in stimulation rate and number of channels on speech understanding in 13 patients with cochlear implants who used the continuous interleaved sampling speech coding strategy. Reducing the stimulation rate from 1,515 to 1,730 pulses per second per channel to 600 pulses per second per channel resulted in decreased overall performance; the understanding of monosyllables and consonants was more affected than the understanding of vowels. Reducing the number of active channels below 7 or 8 channels decreased speech understanding; the identification of vowels and monosyllables was most affected. We conclude that vowel recognition with the continuous interleaved sampling strategy relies on spectral cues more than on temporal cues, increasing with the number of active channels, whereas consonant recognition is more dependent on temporal cues and stimulation rate.

KEY WORDS — channel, cochlear implant, continuous interleaved sampling, speech coding, stimulation rate.

INTRODUCTION

Electrical stimulation of the auditory nerve by means of a cochlear implant has proven to be successful in the rehabilitation of patients who are deaf or have severe hearing impairment. Considerable progress has been made by the introduction of new cochlear implants and speech processing strategies designed to maximize the transmission of information. In this attempt, some fundamental electrophysiological and neurophysiological limitations have to be taken into account.

With present electrode designs, the intracochlear current spread is relatively wide, and adjacent electrodes may stimulate overlapping populations of neural elements. Hence, tuning curves for electrical stimulation are shallower, and tonotopic frequency discrimination is poorer (1 to 3 dB/mm along the basilar membrane for monopolar stimulation, 4 to 13 dB/mm for bipolar stimulation) than they are with acoustic stimulation (>50 dB/mm).¹ Simultaneous or fast nonsimultaneous stimulation of different electrodes may cause channel interactions² and will result in a limited number of perceptually distinct channels for cochlear implants. However, the number of channels that can be useful for optimal speech recognition is still a matter of discussion.

The dynamic range of electrical stimulation of the

auditory nerve is limited to approximately 6 to 30 dB, with great interindividual differences.³⁻⁷ Although the intensity discrimination threshold expressed in decibels has been found to be slightly lower than for acoustic stimulation, the number of discriminable loudness steps within the dynamic range is about 20, compared with 60 to 70 for acoustic stimulation.^{3,4,8,9}

Electrical stimulation results in hypersynchronization of the auditory nerve, especially for stimulation rates in the range below 1,000 Hz. This hypersynchronization will exactly represent the temporal structure of the signal for lower frequencies and may therefore be regarded as advantageous. However, at higher frequencies and suprathreshold stimulation, hypersynchronization and the wide electrical fields result in synchronous excitation of a larger number of neurons. The refractory properties of the auditory nerve will then prevent the exact temporal representation of the signal, as the auditory nerve will not be able to respond to each cycle of the stimulus. This has been shown for sinusoidal as well as for pulsatile stimuli,¹ for which the frequency-following response of the auditory nerve for electrical stimulation is lost for frequencies higher than 400 to 1,000 Hz. For amplitude-modulated pulsatile stimulation, the electrical activity of the auditory nerve shows complex patterns of activity phase-locked to the modulation rate at car-

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TABLE 1. INDIVIDUAL DATA

Patient	Implant	No. of Channels in Standard Condition	Rate in Standard Condition (Hz)	Maximum No. of Channels	Mean Phase Duration (μ s)	Maximum Rate With 4 Active Channels (Hz)
1	C40	7	1,731	7	40	3,030
2	C40	7	1,619	7	44.8	2,702
3	C40	8	1,515	8	40	3,030
4	C40	8	1,515	8	40	3,030
5	C40	8	1,515	8	40	3,030
6	C40	8	1,500	8	40.5	3,000
7	C40	7	1,568	7	47.2	2,564
8	C40	7	1,731	7	50	2,424
9	C40+	8	1,515	12	26.67	4,545
10	C40+	8	1,515	12	26.67	4,545
11	C40+	8	1,515	10	26.67	4,545
12	C40+	8	1,515	12	26.67	4,545
13	C40	8	632	8	98.2	1,234

rier rates between 600 and 3,000 to 4,000 Hz. Beyond carrier rates of approximately 4,000 Hz, the underlying activity seems to be more stochastic, and the nerve activity can lock 1:1 to the modulation frequency.¹⁰ It is still a matter of debate to what extent the auditory nerve can make use of higher pulse rates for perception of temporal cues in the speech signal.

Because of these limitations, speech processing strategies have to be designed to extract the most relevant information from the signal and to choose the appropriate stimulation parameters. More specifically, it is important to understand the contributions of spectral and temporal information to speech recognition in patients with cochlear implants. Psychoacoustic studies with speech signals that contained only limited spectral information have shown that speech recognition could be high with numbers of frequency bands that ranged from 4¹¹ to 8.¹² Current concepts for cochlear implants rely on either a large number of channels with a selected subgroup of electrodes stimulated at relatively moderate rates (eg, the spectral peak [SPEAK] strategy^{13,14}) or fewer channels operating at higher rates (eg, the continuous interleaved sampling [CIS] strategy¹⁵⁻¹⁷). The parameters used clinically are to some extent limited by the technical capacities of the device. A given maximum pulse rate of the device can be distributed among channels. A high number of active channels results in a lower stimulation rate for each individual channel, whereas a lower number of channels will allow for higher pulse rates per channel. A higher number of channels should increase spatial pitch resolution as long as they are perceptually distinct. On the other hand, higher pulse rates may improve the neural representation of temporal information, as long as the central nervous system is able to extract this information.

The present study was designed to investigate the

effect of systematic and independent variations of the stimulation rate and the number of channels on speech understanding with the CIS strategy. We assumed that in the trade-off between the stimulation rate and the number of channels, there might be an optimal combination of parameters. With the enhanced technical properties of the implants, it may become even more important to provide guidelines for programming individual speech processors and directing future developments in this field.

PATIENTS AND METHODS

PATIENTS

Thirteen adult, postlingually deafened patients with cochlear implants were included in the study. All patients were using the CIS strategy as their regular speech coding strategy. Nine patients had the MED-EL COMBI-40 cochlear implant with 8 channels and a maximum stimulation rate of 12,120 pulses per second (pps), and 4 patients had the COMBI-40+ cochlear implant with 12 channels and a maximum stimulation rate of 18,180 pps. Preceding use of the implant ranged from 3 months to 3 years. Initially, all patients — including those with 12-channel implants — were using 7 or 8 channels (channels 1, 2, 3, 4, 6, 8, 10, and 12 for 12-channel implants). In 4 patients (COMBI-40), the most basal channel could not be used. In 1 patient (No. 13), the standard pulse rate with 8 channels was 632 pulses per second per channel (ppsc) because of elevated thresholds. This patient was not included in the final statistical analysis, because his primary parameters of stimulation were much different from those of the rest of the group. The individual numbers of available channels, pulse rates for the standard condition, and maximum available rates with 4 active channels are given in Table 1. The data of patients with 8 channels were pooled with the data of patients with 7 channels in the condi-

TABLE 2. PARAMETERS OF STIMULATION

	No. of Channels			
	4	nstand - 2	7	nstand
Rate of stimulation (ppsc)	1,515-1,730	1,515-1,730	1,515-1,730	1,515-1,730
	1,200	Max		1,200
	600			600
	Max			

nstand — Number of channels in standard settings (in some patients, most basal channel could not be used); ppsc — pulses per second per channel; Max — maximum available stimulation rate.

tion referred to as the standard condition for the calculation of means.

VARIATION OF PARAMETERS

In this study, the stimulation rate and the number of active channels were varied systematically according to Table 2. The parameters were chosen to allow for comparison of various numbers of channels at a constant stimulation rate and of various stimulation rates at a constant number of channels. A channel was defined as a frequency band allocated to a specific electrode. The entire set of parameters, ie, number of channels, stimulation rate, threshold, phase duration of biphasic pulses, and other parameters that are necessary to define a specific program loaded in the speech processor, is referred to below as a map.

Variation of Number of Channels. Starting from the map originally used by patients with either 7 or 8 active electrodes, channels were switched off according to the scheme represented in Table 3 so as to keep the distance of the most basal electrode to the most apical electrode constant and to have an equal spatial distribution of active electrodes along the electrode array insofar as possible. The stimulation rate per channel was kept constant across the active elec-

TABLE 3. SCHEME OF ACTIVE CHANNELS

No. of Channels	Active Channels							
	1	2	3	4	5	6	7	8
8	X	X	X	X	X	X	X	X
7	X	X	X	X	X	X		X
6	X	X	X	X		X		X
4	X			X		X		X

trodes. The overall stimulation rate of the implant across all electrodes diminished in proportion to the number of electrodes switched off.

Variation of Stimulation Rate. The stimulation rate was varied by changing the interstimulus time. It has been shown that thresholds for pulsatile electrical stimulation are a function of pulse rate. Thresholds decrease monotonically with increasing stimulation rate over a range of 100 to 3,000 ppsc.^{4,6} To compensate for the increase in loudness at higher stimulation rates, the most comfortable loudness (MCL) levels and threshold levels of all electrodes were adjusted individually for each stimulation rate by means of a loudness scaling technique.^{18,19} Then, if necessary, final adjustments to the MCL levels were made to obtain equal loudness percepts across all maps. It was found that for pulse rates in the range from 1,200 to 4,500 ppsc, threshold variations were small and rarely exceeded 5% of the dynamic range. At the lowest stimulation rate used (600 ppsc), threshold and MCL levels generally had to be increased (Table 4). The dynamic range varied individually at different pulse rates; mean values did not change significantly (eg, the mean dynamic range decreased by -0.14%, from 1,500 to 1,731 ppsc to 600 ppsc).

Variation of Low-Pass Cutoff Filter Frequency. In the CIS strategy, the microphone signal is converted

TABLE 4. MEAN THR, MCL, AND DYNAMIC RANGE AT 1,500 AND 600 PPS

Patient	THR-600	THR-Std	MCL-600	MCL-Std	DR-600	DR-Std	Diff DR
1	149.3	132.5	552.9	545.7	403.6	413.2	-2.32%
2	145.7	103.9	916.1	916.1	770.4	812.2	-5.15%
3	103.2	121.1	871.8	861.6	768.6	740.5	-3.79%
4	154.2	107.7	840.4	827.9	686.2	720.2	-4.72%
5	138.3	98.8	591.1	541.0	452.8	442.2	2.40%
6	148.4	87.2	756.5	729.5	608.1	642.3	-5.32%
7*	202.1	188.9	644.4	625.4	442.3	436.5	1.33%
8	174.6	165.6	858.1	808.9	683.5	643.3	6.25%
9	359.9	319.0	1,287.5	1,251.9	927.6	932.9	-0.57%
10	181.5	122.0	1,323.0	1,241.8	1,141.5	1,119.8	1.94%
11*	175.6	146.1	951.3	923.9	775.7	777.8	-0.27%
12	115.2	100.4	757.0	735.7	641.8	635.3	1.02%
13†	205.6		608.2				

THR — threshold level; MCL — most comfortable loudness level; THR-600 — threshold at 600 ppsc; THR-Std — threshold at standard condition (1,500 to 1,731 ppsc); MCL-600 — most comfortable loudness level at 600 ppsc; MCL-Std — most comfortable loudness level at standard pulse rate (1,500 to 1,731 ppsc); DR-600 — dynamic range at 600 ppsc; DR-Std — dynamic range at standard pulse rate (1,500 to 1,731 ppsc); Diff DR — difference of dynamic range at 600 ppsc compared with that at 1,500 ppsc (in percent of DR at 1,500 ppsc).

*Patient's pulse duration was 40 μ s instead of 25 μ s.

†Patient had high thresholds and used pulse duration of 80 μ s.

TABLE 5. CONSONANTS AND THEIR CLASSIFICATION

	<i>l</i>	<i>r</i>	<i>m</i>	<i>n</i>	<i>j</i>	<i>v</i>	<i>b</i>	<i>d</i>	<i>g</i>	<i>p</i>	<i>t</i>	<i>k</i>	<i>h</i>	<i>f</i>	<i>s</i>	<i>ʃ</i>
Voicing	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2
Nasality	1	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1
Affrication	1	1	1	1	2	2	1	1	1	1	1	2	2	2	2	2
Duration	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	1
Place	3	6	1	2	4	1	1	2	5	1	2	5	6	3	2	1
Manner	1	1	2	2	3	3	4	4	4	5	5	5	6	6	6	6

from analog to digital and then filtered through a variable number of bandpass filters. The outputs of the filters are rectified and low-pass-filtered for envelope extraction. The envelopes are then used for amplitude-modulating the pulse trains on the electrode allocated to the bandpass filter after appropriate compression.

In the first series of tests, the cutoff frequency of the low-pass filters was constant for all stimulation rates at a cutoff frequency of 400 Hz. This raises the problem that for the lowest stimulation rate tested (600 ppsc), aliasing effects may occur and deteriorate the results. For higher stimulation rates, a cutoff frequency of 400 Hz may limit the benefit of the higher pulse rates by limiting access to rapid temporal changes in the signal. Therefore, in a second series of tests with 6 patients, the cutoff frequency of the low-pass filters was reduced to 200 Hz for a stimulation rate of 600 ppsc (7 or 8 active channels). For the maximum pulse rate in the condition with 4 active channels, the cutoff frequency was increased, with the ratio of stimulation rate to cutoff frequency being held constant at 3.75, ie, the same ratio used at 1,515 ppsc. The results were compared with results obtained with a cutoff frequency of 400 Hz.

SPEECH TESTS

Each patient was given approximately 10 minutes to adjust to each map by listening to numbers and text spoken live-voice. Maps were tested in random order across conditions. Word lists and number lists were randomized for each patient. All tests were delivered from digitized recorded test material in free-field sound-only conditions in a sound-isolated chamber with patients seated 1 m in front of the loudspeaker. Eight different German vowels in a B-vowel-B context (eg, /bab/) and 16 German consonants in an *a*-consonant-*a* context (eg, /aba/), spoken by a male speaker, were presented in random order at 65 dB hearing level. Each vowel and consonant was presented 4 times (Table 5).

For each map, 2 different lists of monosyllabic words of the Freiburg test were tested in a randomized protocol, with each list containing 20 words (20 different lists are available). Two lists of 2-digit numbers of the Freiburg test were tested. The presentation level for the monosyllabic words and numbers was 75 dB

hearing level.

For the second series of tests, which were performed approximately 6 months later, comparing the effect of variations in the low-pass cutoff frequency, 3 lists of monosyllables were tested for each experimental map, randomized across conditions and lists. Because the number of test lists in the Freiburg monosyllabic word test is restricted, lists that had been used in the first series of tests had to be reused. In addition to the vowel-and-consonant tests spoken by a male speaker, recordings of a female speaker were used for each patient and every test condition.

The consonant identification results were analyzed with the "information transmission analysis" developed by Miller and Nicely.²⁰ The confusion matrix is broken down into smaller matrices for specific speech features by grouping the stimuli and responses according to particular speech features. The measure of relative transinformation (TI) is an estimate of how well the information of a specific speech feature is transmitted. The consonants were grouped according to their speech features — *voicing*, *nasality*, *affrication*, *place*, and *duration* — as used by Miller and Nicely²⁰ and Dowell et al.²¹ An additional feature, *manner*, was added.²² The features of the German consonants are listed in Table 5. The TI was calculated for each single consonant test. These values have to be interpreted carefully, because of the small sample size in each single test, which can lead to a bias of values.²⁰ In a second step, the confusion matrices were summed up across subjects for the different test conditions (eg, all consonant confusion matrices of all patients for the condition 4 channels and 600 ppsc), and TI values were calculated for the summed confusion matrices.

STATISTICAL EVALUATION

Normal distribution could not be assumed for all groups of data (Kolmogorov-Smirnov test). Therefore, statistical evaluations were applied by means of nonparametric tests for related samples (Wilcoxon matched pairs test) with the program Statistica (Statsoft Inc). Results were considered statistically significant if the *p* value was <.05. Besides comparing absolute speech test results, we calculated the difference in performance relative to that patient's performance in the defined standard condition, further referred to

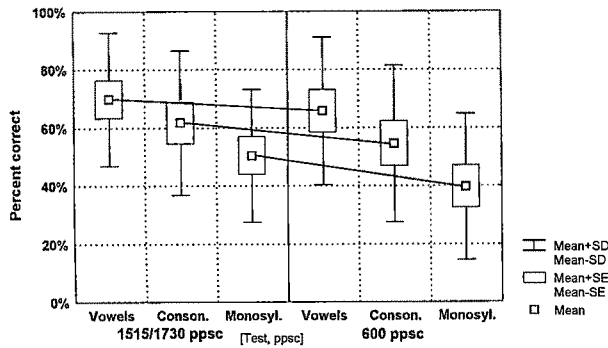


Fig 1. Effect on speech understanding of decreasing stimulation rate from 1,515 to 1,730 pulses per second per channel (ppsc) to 600 ppsc (vowels, consonants, monosyllables) with 7 or 8 active channels. Left side shows mean scores, standard errors, and standard deviations for standard condition; right side shows same for 600 ppsc.

as the "relative performance ratio": $R = [(C_t/C_s) - 1] \times 100$, where R is the relative performance ratio in percent; C_t is the score in the test condition; and C_s is the score in the standard condition. This value was introduced to adjust for the different levels of performance in the standard condition.

RESULTS

Effect of Variation of Stimulation Rate at Constant Number of Channels. With 7 or 8 active channels, reducing the stimulation rate from the standard pulse rate (1,515 to 1,730 ppsc) to 600 ppsc resulted in a decrease of mean performance for monosyllables, vowels, and consonants (Fig 1). The understanding of monosyllables was most reduced ($-9.5\% \pm 9.4\%$; $p < .01$), followed by the understanding of consonants ($-6.2\% \pm 5.1\%$; $p < .01$) and vowels ($-3.2\% \pm 10\%$; $p = .24$). Thus, this effect was statistically significant for monosyllables and consonants, but not for vowels (Table 6). The individual changes in performance are given in Fig 2.

The performance ratio at 600 ppsc relative to the standard condition, defined as 1,515 to 1,730 ppsc (7 or 8 active channels), yielded similar results (Fig

3), with relative differences of $-21.0\% \pm 18.5\%$ ($p < .05$) for monosyllables, $-11.4\% \pm 9.9\%$ ($p < .05$) for consonants, and $-4.5\% \pm 13\%$ ($p > .05$) for vowels (Fig 3). Interindividual differences were considerable and ranged from -55% to $+14\%$ for monosyllables, -34% to 0% for consonants, and -27% to $+14\%$ for vowels.

Changes in the mean scores for decreases of the stimulation rate from the standard rate to 1,200 ppsc were not significant (vowels, $2.4\% \pm 9\%$; consonants, $-0.9\% \pm 9.1\%$; monosyllables, $-3.8\% \pm 12\%$). Also, performance ratios relative to the standard condition at 1,515 to 1,730 ppsc were not significant (vowels, $7.2\% \pm 23.6\%$; consonants, $4.0\% \pm 23.6\%$; monosyllables $-6\% \pm 21.9\%$; Fig 3).

The results obtained with 4 active channels with the standard pulse rate reduced from 1,515 to 1,730 ppsc to 600 ppsc were similar to those obtained with 8 active channels. Consonant understanding was most affected ($-10.6\% \pm 7.1\%$; $p < .01$), followed by monosyllable understanding ($-4.0\% \pm 13.1\%$; $p > .05$) and vowel understanding ($-1.0\% \pm 13.2\%$; $p > .05$; Table 6). The performance ratio was $-16.7\% \pm 16\%$ for consonants ($p < .01$), $-2.6\% \pm 36\%$ for monosyllables ($p > .05$), and $2.9\% \pm 22.7\%$ for vowels ($p > .05$). The interindividual variations were greater than for the condition with 7 or 8 active channels.

With 4 active channels, the stimulation rate can be increased up to a maximum of 3,030 ppsc (COMBI-40) or 4,545 ppsc (COMBI-40+); the exact rate depends on the individual thresholds and pulse durations. For this test, the maximum available rate in each patient was chosen, resulting in a mean rate of 3,390 ppsc, with a range from 2,424 to 4,545 ppsc. (Patient 13 was not included, because his maximum pulse rate differed considerably from those of the other patients.) Increasing the stimulation rate from the standard pulse rate of 1,515 to 1,730 ppsc to a mean rate of 3,390 ppsc resulted in a modest increase in mean scores (vowels, $2.9\% \pm 15.4\%$; consonants, $1.5\% \pm$

TABLE 6. DIFFERENCES IN PERFORMANCE FOR DIFFERENT STIMULATION RATES

Parameters	Vowels			Consonants			Monosyllables			n
	Mean Difference	SD of Differences	p	Mean Difference	SD of Differences	p	Mean Difference	SD of Differences	p	
1,515/1,700 → 600 ppsc, 7/8 ch*	-3.2%	10.0%	.2393	-6.2%	5.1%	.0077	-9.5%	9.4%	.0096	12
1,515/1,730 → 1,200 ppsc, 7/8 ch	2.4%	9.0%	.6103	-0.9%	9.1%	.6744	-3.8%	12.1%	.4148	10
1,200 → 600 ppsc, 8 ch	-6.0%	10.9%	.1387	-5.3%	10.3%	.1387	-6.1%	13.7%	.2135	10
1,515/1,730 → 600 ppsc, 4 ch	-1.0%	13.2%	.6891	-10.6%	7.1%	.0033	-4.0%	13.1%	.5937	12
1,515/1,731 → Max ppsc, 4 ch*	2.9%	15.4%	.5937	1.5%	8.8%	.6465	1.4%	14.7%	.5937	12
1,515/1,731 → Max ppsc, 4 ch†	8.7%	10.6%	.1400	9.9%	4.8%	.0680	9.5%	5.3%	.0680	4
600 → Max ppsc, 4 ch*	3.9%	19.0%	.5633	12.1%	12.6%	.0108	5.4%	12.3%	.2094	12

*Including test results of second series of tests.

†Including only patients using COMBI-40+ implant with maximum stimulation rate (Max) of 4,545 ppsc at 4 active channels (ch).

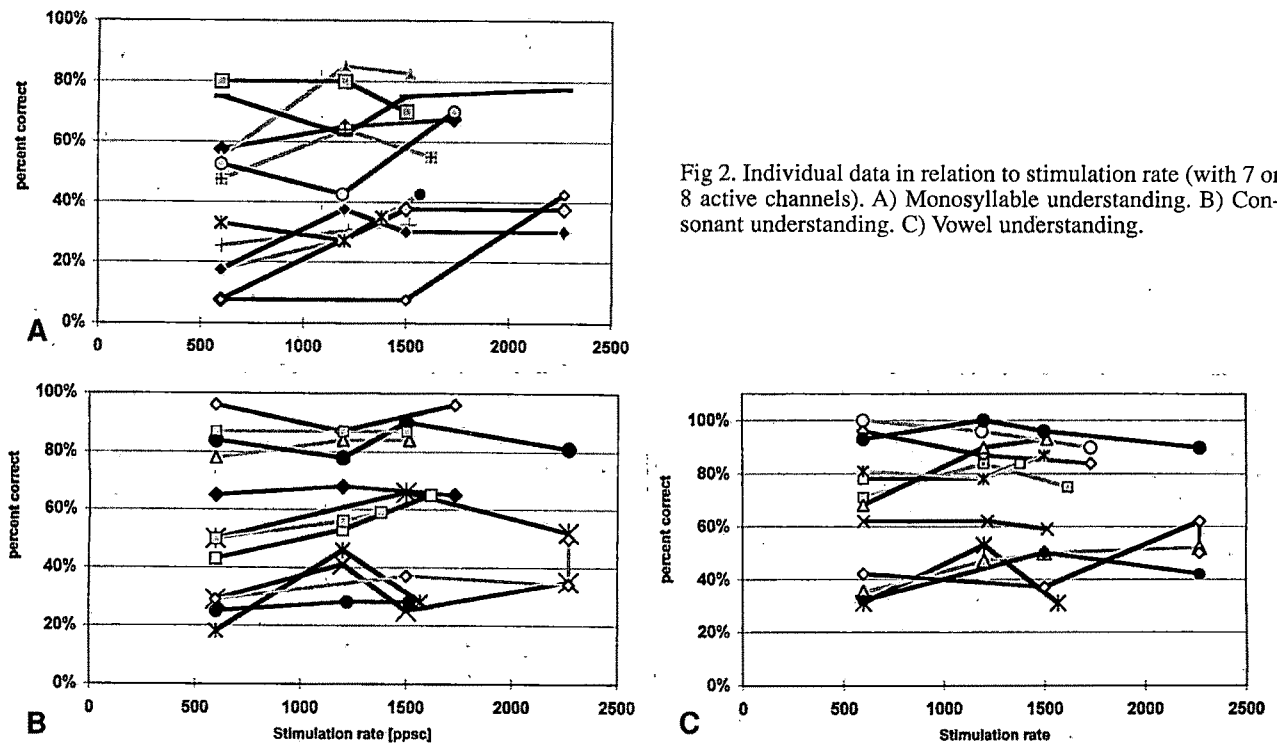


Fig 2. Individual data in relation to stimulation rate (with 7 or 8 active channels). A) Monosyllable understanding. B) Consonant understanding. C) Vowel understanding.

8.8%; monosyllables, $1.4\% \pm 14.7\%$; Table 6) that was not statistically significant. Performance ratios were not significant: $6.5\% \pm 18.4\%$ for vowels ($p > .05$), $5.8\% \pm 20.1\%$ for consonants ($p > .05$), and $14.6\% \pm 30.8\%$ for monosyllables ($p > .05$).

In the 4 patients who were using the COMBI-40+ cochlear implant with a maximum stimulation rate of 18,180 pps, the maximum available pulse rate per channel was 4,545 pps. For these patients alone, an increase from 1,500 pps to 4,545 pps improved the understanding of monosyllables by $9.5\% \pm 5.3\%$ ($p = .068$), of consonants by $9.9\% \pm 4.8\%$ ($p = .068$), and of vowels by $8.7\% \pm 10.6\%$ ($p = .14$). These changes were larger than those for the group of patients who had the COMBI-40 cochlear implant with

a maximum stimulation rate of 12,120 pps.

No statistical correlation between the level of mean scores in the standard condition (7 or 8 active channels, 1,500 to 1,730 pps) and the changes in mean scores (absolute difference) from 1,500 to 1,730 pps to the maximum available rate could be observed. Comparing the results at 3,390 pps to those at 600 pps with 4 active channels showed significantly higher intelligibility of consonants at 3,390 pps ($12.1\% \pm 12.6\%$, $p = .01$) and nonsignificantly higher intelligibility of monosyllables ($5.4\% \pm 12.3\%$; $p > .05$) and vowels ($4.3\% \pm 19.0\%$; $p > .05$).

In the condition with 5 or 6 active channels ($n = 2$), increasing the stimulation rate from 1,500 to 1,730 pps to the maximum stimulation rate (mean, 2,200 pps) did not result in significant changes (consonants, $2.3\% \pm 17.0\%$, $p > .05$; vowels, $1.6\% \pm 15.8\%$, $p > .05$; monosyllables, $-2\% \pm 11.0\%$, $p > .05$; Table 6).

In 4 patients who used the 12-channel implant with a maximum stimulation rate of 18,180 pps, the pulse rate with 8 active channels could be increased to 2,272 pps. Compared with the standard condition with 1,515 pps, the understanding of monosyllables increased by $10\% \pm 12.0\%$, that of consonants increased by $4.8\% \pm 9.8\%$, and vowel understanding remained unchanged. These results were not statistically significant.

In the condition of 7 or 8 active channels at a standard pulse rate compared with 4 active channels at

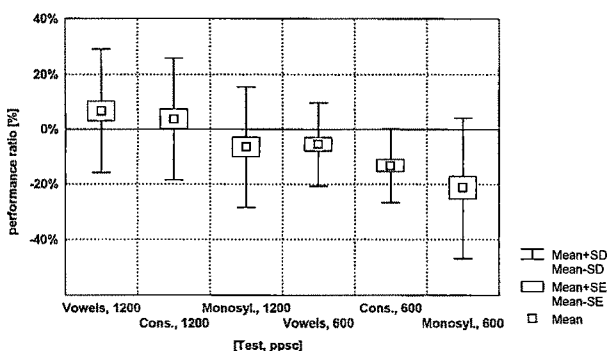


Fig 3. Performance ratios relative to standard condition (7 or 8 channels, 1,500 pps) for variations of stimulation rate (1,200 and 600 pps). Mean values, standard errors, and standard deviations of performance ratios are shown for vowel, consonant, and monosyllable recognition.

TABLE 7. DIFFERENCES IN PERFORMANCE FOR DIFFERENT CUTOFF FREQUENCIES OF LOW-PASS FILTERS

Parameters, Including Cutoff Frequency	Vowels (Male)		Vowels (Female)		Consonants (Male)		Consonants (Female)		Monosyllables	
	Diff	p	Diff	p	Diff	p	Diff	p	Diff	p
400 Hz → 200 Hz, 8 ch, 600 ppsec	-0.8%	.7	-3.8%	.2	1.8%	.7	3.1%	.29	1.3%	.64
400 Hz → Adapted, 4 ch, Max rate	10.8%	.2	2.6%	.4	2.0%	.08	1.0%	.8	-1.8%	.69

Absolute differences in performance with different cutoff frequencies of low-pass filters (n = 6). With 7 or 8 channels (ch) at 600 ppsec, cutoff frequencies used were 400 Hz and 200 Hz, and with 4 active channels at maximum stimulation rate, cutoff frequencies used were 400 Hz and individually adapted cutoff frequency with ratio of stimulation rate/cutoff frequency of 3.75. Individually adapted cutoff frequency was chosen because maximum stimulation rates ranged from 2,500 to 4,545 ppsec.

the maximum pulse rate, the overall stimulation rate of the implant is constant. Moving from the 7- or 8-channel condition with the standard stimulation rate to the 4-channel condition with the maximum stimulation rate, the understanding of vowels was reduced ($-9.4\% \pm 14\%$; $p = .059$), as was that of monosyllables ($-6.5\% \pm 9.2\%$; $p = .033$) and consonants ($-2.6\% \pm 8.4\%$; $p = .299$).

Effect of Variation of Cutoff Frequency of Low-Pass Filters. In a second series of tests, the effect of varying the cutoff frequency of the low-pass filters was studied. In 6 patients, the cutoff frequency was reduced to 200 Hz at a pulse rate of 600 ppsec with 7 or 8 active channels. Results were compared with results obtained at a cutoff frequency of 400 Hz under otherwise constant conditions. In the 200-Hz condition, consonant understanding slightly increased (3.1% for female speaker consonants, 1.8% for male speaker consonants), vowel understanding decreased (-3.8% for female speaker vowels, -0.8% for male speaker vowels), and monosyllable understanding increased by 1.3% (Table 7). Yet, none of these changes were statistically significant, and they could not account for the differences found when the stimulation rate was varied at a constant cutoff frequency.

Adjusting the ratio of stimulation rate to cutoff frequency to 3.75 for the maximum stimulation rate (with 4 active channels) increased understanding of vowels (10.8% for male speaker vowels, 2.6% for female speaker vowels) and consonants (2.0% for male, 1.0% for female) and slightly reduced understanding of monosyllables (-1.8%; Table 7) as compared with the cutoff frequency of 400 Hz. None of these changes were statistically significant.

Effect of Variation of Channel Number at Constant Pulse Rate. The number of channels was varied with the stimulation rate held constant. The standard condition was defined as either 7 or 8 active channels. Of the 4 patients with the 12-channel version of the implant, only 2 patients could be tested with 12 channels: 1 patient had only 10 channels available, and another patient was not tested with 12 channels because of time constraints. At a constant pulse rate of 1,500 to 1,730 ppsec, reducing the number of channels from 7 or 8 to 4 decreased understanding of vowels ($-11.8\% \pm 12.5\%$; $p = .012$), monosyllables ($-8.0\% \pm 6.9\%$; $p < .01$), and consonants ($-4.1\% \pm 8.6\%$; $p > .05$; Table 8 and Fig 4). These differences were statistically significant for vowels and monosyllables. There were important interindividual differences. The individual results are shown in Fig 5. Similar results were obtained when decreasing the number of channels from the standard condition (7 or 8 channels) to n - 2 channels (ie, 5 or 6 channels) at 1,515 to 1,730 ppsec and when the number of channels was reduced from 8 to 4 at 600 ppsec (Table 8), but these changes were not significant. The performance ratios for variations of channel numbers relative to the standard condition (7 or 8 channels, 1,515 ppsec) are shown in Fig 6. Increasing the number of channels to more than 8 generally did not increase test scores in the 3 patients tested. Only in 1 patient did we observe an increase in monosyllable understanding.

Results of Information Transmission Analysis for Consonants. The results of consonant understanding have been further submitted to information transmission analysis. In the first step, scores of TI were calculated for each individual consonant confusion ma-

TABLE 8. DIFFERENCES IN PERFORMANCE FOR DIFFERENT NUMBERS OF CHANNELS

Parameters	Vowels			Consonants			Monosyllables			n
	Mean Difference	SD of Differences	p	Mean Difference	SD of Differences	p	Mean Difference	SD of Differences	p	
7/8 ch → 4 ch, 1,515/1,730 ppsec*	-11.8%	12.5%	.0121	-4.1%	8.6%	.1141	-8.0%	6.9%	.0077	12
7/8 ch → n - 2 ch, 1,515/1,730 ppsec	-9.3%	19.9%	.1823	-4.6%	8.8%	.1361	-4.0%	10.2%	.2478	12
n - 2 ch → 4 ch, 1,515/1,730 ppsec	0.3%	16.8%	.7598	2.8%	9.2%	.3505	-2.9%	12.0%	.3329	12
7/8 ch → 4 ch, 600 ppsec*	-7.1%	15.1%	.1307	-6.3%	8.5%	.0844	2.7%	13.0%	.6379	12

*Includes test results of second series of tests.

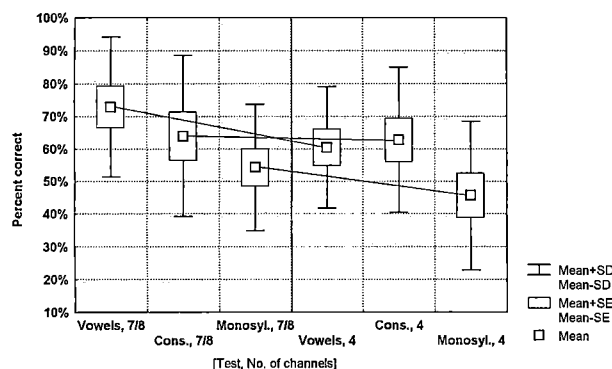


Fig 4. Effect of decreasing number of channels from 7 or 8 to 4 on speech understanding (vowels, consonants, and monosyllables) at standard stimulation rate (1,515 to 1,730 pps). Left side shows mean scores, standard errors, and standard deviations for standard condition (7 or 8 channels); right side shows same for 4 active channels.

trix for every patient and test condition. The test results were compared by the Wilcoxon matched pairs test. Significant differences were found for reduction in stimulation rate (7 or 8 channels; 1,515 to 1,731 pps, as compared to 600 pps) for overall TI and the feature *voicing*. A reduction of TI for the feature *place* could be seen with 4 active channels with the stimulation rate reduced from the standard rate to 600 pps. Reduction of the number of channels from 7 or 8 to 4 at the standard pulse rate did not show significant changes in overall TI or TI of consonant features. At 600 pps, reduction of the number of channels from 7 or 8 resulted in a significant decrease of TI of the features *place* and *duration*. In the second

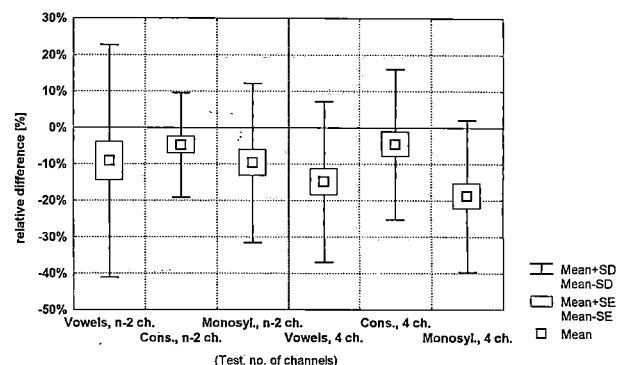


Fig 6. Performance ratios relative to standard condition (7 or 8 channels, 1,500 pps) for variations of number of channels (5 or 6 [ie, $n-2$] and 4 channels). Mean values, standard errors, and standard deviations of performance ratio are given for vowel, consonant, and monosyllable recognition.

step of analysis, the consonant confusion matrices for a specific test condition were pooled across patients. The results of TI are given in Table 9. The reduction of the stimulus rate from the standard rate to 600 pps resulted in a reduction of overall TI (-5.3%) and transmission of all feature information, especially *voicing* (-11.8%), *manner* (-4.8%), and *duration* (-7.0%). A similar reduction was found in comparing the standard rate with 600 pps at 4 channels (TI, -7.2%).

Increasing the rate from the standard rate to the maximum available rate increased total information transmission (3.2%) and information transmission of all features, especially *manner* (11.7%) and *affrica-*

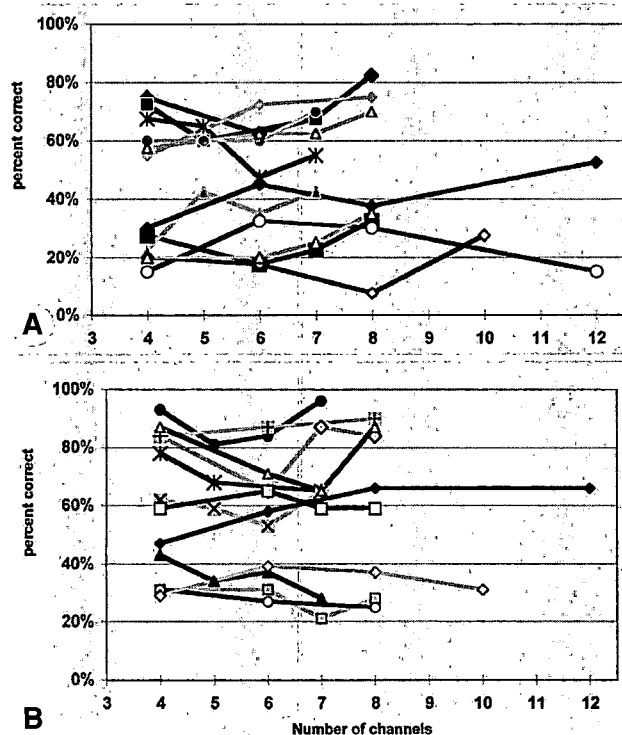


Fig 5. Individual data in relation to number of channels (at standard pulse rate). A) Monosyllable understanding. B) Consonant understanding. C) Vowel understanding.

TABLE 9. RELATIVE TRANSINFORMATION FOR CONSONANTS

Rate	No. of Channels	Total	Voicing	Manner	Nasality	Place	Duration	Affrication
Standard (1,515-1,730 ppsc)	7/8	53.82%	48.30%	52.12%	48.39%	31.28%	39.95%	47.73%
600 ppsc	7/8	48.51%	36.62%	47.35%	45.47%	29.57%	32.98%	43.62%
Standard (1,515-1,730 ppsc)	4	53.90%	42.34%	49.96%	42.36%	35.06%	34.63%	46.63%
600 ppsc	4	46.70%	34.26%	45.80%	31.42%	24.83%	20.65%	38.29%
Maximum rate	4	57.12%	45.12%	61.69%	54.75%	36.23%	28.01%	63.07%

tion (16.44%). A reduction of the number of channels from 7 or 8 to 4 channels at the standard pulse rate had little effect on total TI (0.1%) or the TI of *affrication* (-1.1%). The transmission of the features *voicing* (-6.0%), *manner* (-2.16%), and *duration* (-5.3%) was reduced. Reduction of the number of channels at 600 ppsc yielded a decrease of TI (-1.81%).

Individual Test Results and Optimized Conditions. Although statistically significant changes in speech intelligibility in relation to different parameters have been found for the overall group of subjects, interindividual differences were large, and in some cases, individual changes in performance clearly deviated from the group trend (Figs 2 and 5). This also becomes obvious when we consider the relatively large standard deviations for the differences between different conditions. Apart from the analysis of the group changes, optimal combinations of parameters for each individual patient can be found in the limits of the implant. They can be optimal either for a single recognition task, eg, consonants, or for the combined performance. For the purpose of representing the overall performance, a mean of consonant, vowel, and monosyllable intelligibility was calculated and combined in a compound score. In Table 10, mean compound scores of the overall group of patients are given for the different conditions. The best results were obtained in the condition with 7 or 8 channels and 1,200 ppsc, in the condition with 7 channels and 1,515 to 1,731 ppsc, and in the standard condition with 7 or 8 channels and 1,515 to 1,731 ppsc.

In Table 11, the optimal combinations of parameters for each individual patient are given. In some

TABLE 10. MEAN COMPOUND SCORES FOR DIFFERENT CONDITIONS

Rate	No. of Channels	N	Mean	SD
Standard	7/8	12	60.6%	22.1%
1,200 ppsc	7/8	10	64.2%	18.1%
Standard	7	8	61.4%	19.1%
600 ppsc	7/8	12	53.3%	24.2%
Standard	n - 2	12	54.7%	17.9%
Maximum	n - 2	12	55.3%	15.4%
Maximum	4	12	56.7%	15.0%
Standard	4	12	54.8%	19.5%
600 ppsc	4	12	49.6%	19.1%

patients, several conditions were equivalent in the result. Four of the 13 patients performed best in the so-called standard condition, 4 patients had better results with a reduced number of channels and higher pulse rates, and 3 patients performed best or equally well with a pulse rate of 600 ppsc. In 2 of 4 patients with 12-channel implants, 12 channels at the standard pulse rate were superior to 8 channels.

DISCUSSION

The speech signal can be regarded as a continuously and rapidly changing acoustic event in time. It can be analyzed with the focus on its spectral components or on its temporal structure. Most consonants are short acoustic events with rapid changes in amplitude and spectrum. Even vowels have steady-state spectra limited to only a few milliseconds, with important transitional parts between consonants and vowels or different vowels. Therefore, one may hypothesize that the exact temporal representation of the speech signal is at least as important as its spectral representation by tonotopicity, and that limitations in one factor or the other may influence the different aspects of speech recognition. In the normally functioning cochlea, the signal is analyzed on the basis of tonotopic representation of different frequencies at different locations along the basilar membrane on one hand, and the representation of temporal struc-

TABLE 11. INDIVIDUAL MAXIMA OF SPEECH INTELLIGIBILITY

Patient No.	No. of Channels	Pulse Rate (ppsc)
1	7	1,200
	7	600
	4	1,731
2	5	1,619
3	8	1,515
4	4	602
5	8	1,515
6	8	600
7	4	2,564
8	7	1,731
9	12	1,500
	8	1,200
10	12	1,500
11	8	2,272
12	6	3,030
13	8	395

tures by temporal variations of the amplitude in one location on the other hand. The two processes are closely interrelated, and nonlinear interactions exist between them.

In electrical stimulation of the cochlea, the analysis is performed outside the cochlea by the speech processors, and the parameters can be chosen independently by using different filtering parameters and stimulation parameters. A very important step is the signal transmission from the electrical stimulus to the auditory nerve, because this is subject to several limitations, described in the Introduction. Important parameters in this process are the stimulation rate and the number of channels. Varying the stimulation rate in cochlear implants will probably affect the temporal resolution of the speech signal, as long as the auditory nerve is able to represent the temporal structure, whereas varying the number of channels will primarily affect the spectral resolution by tonotopic frequency discrimination, as long as different subpopulations of the auditory nerve that are perceived as different are excited. Because of the limiting factors of electrical stimulation of the auditory nerve, maxima of discriminable channels and of usable stimulation rate might exist.

In the present study, the effects of systematic and independent variations of stimulation rate and number of channels for the CIS strategy were investigated. From the statistical analysis of the data obtained in the present study, the following conclusions can be drawn.

Reducing the stimulation rate from the standard pulse rate (1,515 to 1,730 ppsc) to 600 ppsc decreased overall performance; the understanding of monosyllables and consonants was more affected than the understanding of vowels. In regard to information transmission for consonants, a decrease of overall TI and the TIs of *voicing* and *place* has been observed. Increasing the pulse rate beyond the standard pulse rate resulted in a general but nonsignificant increase in mean scores for vowels, consonants, and monosyllables, as well as in total information transmission for consonants. However, in patients in whom the stimulation rate could be raised to 4,545 ppsc with 4 active channels (COMBI-40+), a greater increase in mean scores could be observed.

A tentative explanation might be seen in neural response data from sinusoidally amplitude-modulated pulse trains obtained by Wilson.²³ He reports that when the pulse rate is increased considerably, toward 5,000 ppsc or beyond, neural responses become more and more stochastic, so that they follow the envelope of the pulse train more accurately. The more accurate representation of the sinusoidally amplitude-modu-

lated waveform should be beneficial for detection of rapid temporal changes. Pulse rates even higher than 4,000 ppsc may be needed to see further increases in speech understanding with the CIS strategy.

It is interesting to consider the overall stimulation rate of the implant (pulse rate per channel $\times$ number of channels), which might be a relevant parameter. In moving from the 8-channel condition to the 4-channel condition at a constant overall stimulation rate, consonant understanding was only slightly reduced, whereas vowel and monosyllable understanding decreased, albeit to a lesser extent than the decrease caused by reducing the number of channels at a constant pulse rate per channel and a reduced overall pulse rate.

In the range tested, varying the cutoff frequency of the low-pass filters for a stimulation rate of 600 ppsc had no significant effect on speech recognition. Neither were significant differences found for increases of the cutoff frequency at the maximum stimulation rate with 4 channels. This observation is in accordance with results obtained by Shannon et al¹¹ in subjects with normal hearing, listening to speech signals that were processed in a way quite similar to the CIS strategy, who did not show significant differences for variations of the low-pass filters in the range from 50 to 500 Hz.

Reducing the number of active channels from 7 or 8 to 4 at the standard pulse rate decreased speech understanding, with the understanding of vowels and monosyllables being most affected. In regard to information transmission of consonants, no significant changes were observed.

Whereas these data confirm the results of Shannon et al¹¹ in listeners with normal hearing with respect to consonants, which did show near-maximum understanding with 4 channels, they differ with respect to vowel understanding. We found a statistically significant effect comparing the conditions with 4 and 8 channels, indicating that vowel recognition relies more on spectral cues than consonant recognition and that cochlear implant patients can make use of more than 4 channels for their perception. These results are in accordance with results obtained by Fishman et al²⁴ with the SPEAK strategy. They measured speech recognition as a function of the number of channels with the SPEAK strategy. Consonant and sentence understanding reached near-maximum with 4 electrodes, whereas vowel understanding and monosyllable understanding reached near-maximum at 7 electrodes. No differences were observed on any test among the 7-, 10-, and 20-electrode conditions. The pulse rate per electrode was not held constant in their study, but increased with reduction in the number of

channels. Therefore, independent assessment of the effects of the stimulation rate was not possible. The lack of further improvement with channel numbers greater than 7 is confirmed by a previous study by Kileny et al,²⁵ who compared speech recognition in 7 patients using either the entire 20 electrodes or only the 10 basal electrodes of the Nucleus-22 cochlear implant with the F0F1F2 speech coding strategy. They found no significant differences between the two conditions, although a trend to better performance on open-set measures was observed with 20 electrodes. Geier and Norton²⁶ removed the 5 basal, the 5 apical, or the 5 middle electrodes in 5 subjects (Nucleus-22 Mini cochlear implant, F0F1F2 strategy). Only removal of the apical electrodes resulted in decreased performance in 3 of the 5 subjects tested, but this might be attributed to a loss of spectral information in the high-frequency range, and not necessarily to the number of channels.

For the percutaneous Symbion/Ineraid cochlear implant with a compressed analog strategy, consonant recognition in relation to number of channels was measured by Dorman et al²⁷ in 10 subjects. A maximum of 4 channels, selected from the available 6 contacts, were tested. Channels were simply switched off from basal to apical without redistributing the spectral information across the remaining electrodes. Consonant understanding increased up to 4 channels in this study, but it was also concluded that high levels of consonant recognition could probably be achieved by 2 channels situated in the basal and the apical regions. This result is in accordance with the results of the present study; ie, consonant intelligibility was less affected by reductions in the number of channels than vowel recognition.

Studies with the CIS strategy were performed with the Ineraid electrode by Lawson et al²⁸ and Dorman and Loizou.²⁹ In 1 patient, Lawson et al found an increase in consonant understanding up to 6 channels, the highest number tested. Similar results were obtained by Dorman and Loizou in a single patient who found a monotonic increase of vowel and consonant intelligibility up to 6 channels. Performance was significantly better with 6 channels than with 4 channels. In our study, the intelligibility of consonants was not significantly affected in the comparison of 7 or 8 channels to 4 channels.

Other studies with the CIS strategy were reported by Brill et al³⁰ and Lawson et al.³¹ They found that consonant and sentence understanding reached near-maximum with 4 electrodes, whereas vowel understanding and monosyllable understanding reached near-maximum at 7 electrodes. No differences were observed on any test among the 7-, 10-, and 20-electrode

conditions. These results are in accordance with the results of this study. With the percutaneous Nucleus-22 electrode array, Lawson et al studied the effect of variations in the number of channels, stimulation rate, and other parameters on consonant recognition with the CIS strategy in 10 subjects. Whereas consonant recognition increased from 1 to 4 channels, no clear further improvement was seen beyond 4 electrodes (up to 20). Reducing the rate below 833 ppsc decreased the consonant recognition.

The similarity of results of the studies by Dorman and Loizou,²⁹ Lawson et al,^{28,31} Brill et al,³⁰ and Fishman et al²⁴ to those of the present study suggest that although different speech coding strategies were used, with coding strategies based on representation of temporal changes in a distinct number of channels of stimulation, consonant recognition is based on temporal cues in relatively few frequency bands (around 4), whereas for vowel recognition, more detailed spectral cues are important, and up to 7 or 8 channels can be used by patients with cochlear implants.

Because all conditions of stimulus parameters were tested during acute experiments, patients had only a short time to adjust to the different conditions, and learning effects could not be assessed. The results may therefore be biased by the habits of hearing through the implant with the parameters used in everyday life, and these parameters may be expected to have some advantage compared to other settings of parameters.

With a reduced number of channels, different subsets of active channels can be chosen. It has been shown that different subsets with equal numbers of channels can yield different results for speech understanding. An attempt has been made to select the optimized subset on the basis of maximum pitch discriminability in the channels used.²⁴ In general, the results indicate that performance could be increased by choosing the optimized subset. In regard to this study, in which this attempt was not made, we would expect increased performance in some of the conditions with fewer active channels, and an advantage with higher pulse rates for some of the patients.

Individual patients may show patterns of performance different from those of the overall group. Some patients may be able to use a higher number of channels, whereas others may benefit more from higher stimulation rates. It is of importance to determine the optimal combination of parameters for an individual patient.

We may conclude from the results of this study that the understanding of consonants strongly relies on the perception of temporal cues, whereas vowel

intelligibility depends more on tonotopic cues. The temporal cues are transmitted by the CIS strategy and depend on the stimulation rate per channel. Patients with cochlear implants are able to benefit from higher stimulation rates (1,500 ppsc and greater) for per-

ceiving these temporal cues. The tonotopic cues are influenced by the number of stimulation channels. Reducing the number of channels down to 4 only slightly reduces consonant recognition, whereas vowel recognition is significantly affected.

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EFFECT OF ADENOVIRUS TYPE 1 AND INFLUENZA A VIRUS ON *STREPTOCOCCUS PNEUMONIAE* NASOPHARYNGEAL COLONIZATION AND OTITIS MEDIA IN THE CHINCHILLA

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Considerable evidence has implicated respiratory tract virus potentiation of bacterial adherence, colonization, and superinfection as a significant factor contributing to the pathogenesis of otitis media (OM). Influenza A and B viruses, adenovirus, and respiratory syncytial virus are the primary respiratory tract viruses associated with this disease. Investigations have established a dramatic increase in the development of experimental OM in chinchillas co-inoculated with influenza A virus and *Streptococcus pneumoniae* (Spn). The mechanism underlying this phenomenon was suggested to involve, in part, viral compromise of eustachian tube mucosal integrity and function. This study was designed to assess and compare the effect of adenovirus and influenza A virus infection on adherence, the kinetics of colonization, and invasion of the middle ear by Spn in the chinchilla model of OM. Cohorts were inoculated intranasally with adenovirus type 1 or influenza A virus, and then inoculated intranasally 7 days later with Spn 6A. All cohorts were observed over a 14-day period after challenge with Spn, and the incidence and severity of OM were assessed by several methods, including culture of the nasopharynx and middle ear effusions. The data indicated that influenza A virus promotes a significant increase in nasopharyngeal colonization by Spn, an increased incidence and severity of OM, and a sustained presence of Spn in the effusions. Adenovirus infection, however, did not enhance colonization by Spn or result in an increased incidence or severity of OM.

KEY WORDS — adenovirus, influenza A virus, otitis media, *Streptococcus pneumoniae*.

INTRODUCTION

Streptococcus pneumoniae (Spn) is the bacterial pathogen most frequently isolated from middle ear fluid (MEF) specimens of children with otitis media (OM) and accounts for 20% to 50% of cases of this disease. Experimental and clinical studies suggest that influenza A virus promotes Spn-induced OM, although a mechanism for this synergistic interaction has not been completely defined. Enhanced susceptibility to bacterial diseases in patients with influenza virus infection may be due to a variety of causes, including but not limited to viral disruption of airway homeostasis, disruption of mucociliary clearance, enhanced adherence of bacterial pathogens to virus-infected or damaged cells, and, in the case of OM, eustachian tube dysfunction.^{1,2} Giebink et al³ reported that influenza virus infection promotes the development of OM in chinchillas colonized with Spn and hypothesized that the development of negative pressure in the middle ear (ME) is a significant component of this synergistic interaction.

Adenovirus is also among the upper respiratory

tract viruses most often associated with OM⁴ and was identified as the virus most frequently isolated in approximately 1,200 episodes of acute OM.⁵ The mechanisms by which adenovirus predisposes to nontypeable *Haemophilus influenzae* (NTHi)-induced OM have also been the focus of several studies^{6,7}; however, no data are available regarding the interaction between adenovirus and Spn OM strains in vivo.

Viral potentiation of bacterial adherence and colonization relative to OM pathogenesis is of particular interest and was detailed in a recent review.⁸ Viral infection can induce the expression of viral proteins on the eukaryotic cell surface that serve as receptors, and can also alter cell surface glycoconjugates, exposing bacterial binding sites.^{9,10} Finally, virus-induced damage of the respiratory epithelium and the process of tissue regeneration are two other mechanisms by which viral infection creates new binding sites for bacteria or expresses additional ones.²

Several reports have been published on the role of influenza A¹¹⁻¹⁴ and adenovirus^{6,7} in the pathogenesis of OM. The purpose of this study was to compare

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and assess the effect of an antecedent adenovirus type 1 or influenza A virus infection on the ability of Spn type 6A (Spn 6A) to colonize the nasopharynx, ascend the eustachian tube, and invade the ME in vivo in the chinchilla model.

MATERIALS AND METHODS

Experimental Design. Two separate investigations were performed. First, we evaluated the effect of adenovirus. An experimental cohort comprising 15 chinchillas was inoculated intranasally with adenovirus and 7 days later given an intranasal challenge with Spn 6A. A control cohort received diluent without virus. Three chinchillas, preselected and randomized, from each cohort were evaluated for nasopharyngeal colonization and OM at each of 5 different time periods after Spn 6A inoculation as described below. Each chinchilla was sampled only once. The entire experiment was repeated with influenza A virus instead of adenovirus. The abilities of each virus to promote nasopharyngeal colonization, invasion of the ME, and induction of Spn OM were compared. All experiments were performed in duplicate.

Animals. Sixty healthy chinchillas (*Chinchilla laniger*; 220 to 450 g), free of ME disease as determined by otoscopy and tympanometry, were used in these studies.

Virus Inoculations. Adenovirus type 1^{6,7} and influenza virus A/Alaska/6/77(H3N2)^{12,14} have previously been described in detail. The virus stocks were diluted and suspended in sterile Eagle's minimal essential medium (MEM; Whittaker MA Byproducts, Walkersville, Md). Two cohorts of 15 chinchillas each were inoculated intranasally with 0.2 mL of a virus suspension containing approximately 6×10^6 median tissue culture infective doses per milliliter of adenovirus type 1 or 6×10^6 plaque-forming units of influenza A virus per milliliter. The inoculum was divided equally between the two nares. Two cohorts of 15 chinchillas each received 0.2 mL of MEM without virus and served as the controls for each experiment. All virus-inoculated animals were housed separately from those that received only MEM.

Bacterial Inoculation. For these experiments, we used Spn 6A (EF3114, kindly provided by Dr B. Andersson, Department of Clinical Immunology, University of Göteborg, Sweden), which has been described in detail previously.^{15,16} Log-phase cultures were prepared from chocolate agar plate subcultures by inoculating Todd-Hewitt broth (Sigma, St Louis, Mo) with Spn 6A grown overnight on chocolate agar and obtained by washing the plates with 5 mL of Dulbecco's phosphate-buffered saline solution (D-PBS). After a 3-hour incubation, the cultures were

centrifuged at 3,500g for 20 minutes, washed twice, and resuspended in D-PBS. The concentration of Spn was determined by standard colony plate count. Seven days after challenge with either virus, the virus-infected and control chinchillas were inoculated intranasally with 0.5 mL of the Spn 6A suspension containing 5×10^6 colony-forming units (CFU) per milliliter. All virus-inoculated animals were housed separately from controls that received Spn 6A only.

Disease Course Assessment. All assessments were made blindly and by the same observers throughout this study. Tympanic membrane (TM) inflammation was assessed in both ears of each chinchilla daily by means of otoscopy using a modification of the rating scale described previously.^{7,17} For these experiments, inflammation was rated on a scale of 0 to 4+ with half-step increments (0 = normal with no inflammation; 0.5 = minimal erythema with >50% of the TM inflamed; 1.0 = slight erythema with slight retraction; 1.5 = slight to moderate erythema; 2.0 = moderate erythema with moderate retraction or bulging and slight middle ear effusion [MEE]; 2.5 = moderate to significant erythema with moderate to significant retraction and moderate MEE; 3.0 = significant erythema, retraction, and moderate to significant MEE; 3.5 = significant to severe erythema, retraction, and MEE; and 4.0 = perforated TM with severe inflammation). Middle ear pressure (MEP) changes were evaluated daily in both ears of each chinchilla for up to 14 days after inoculation with Spn 6A by means of tympanometry (Ear Scan, Micro Audiometric, South Daytona, Fla). Normal chinchilla MEP was considered to be between -60 daPa and +40 daPa.¹⁸

Nasopharyngeal Colonization and Invasion of ME. Three chinchillas, preselected and randomized, were evaluated by tympanocentesis and nasopharyngeal lavage on days 1, 3, 7, 10, and 14 after inoculation with Spn 6A as previously described.⁷ Tympanocentesis was first performed on both ears of each of the 3 chinchillas by aspiration with a tuberculin syringe fitted with a 25-gauge needle. If no MEF was present, the bullas were lavaged with 0.5 mL of prewarmed sterile saline solution. After tympanocentesis, nasopharyngeal lavage was performed on each chinchilla as described previously.^{6,14} Chinchillas were not subjected to repeated tympanocentesis or lavages. Tympanocentesis and bulla lavage were always performed before nasopharyngeal lavage to prevent contamination of the ME. The MEF or ME lavages and nasal lavages were cultured on chocolate agar plates and incubated overnight in a humidified atmosphere with 5% CO₂, and the number of CFU per milliliter was determined by standard dilution and plate count.

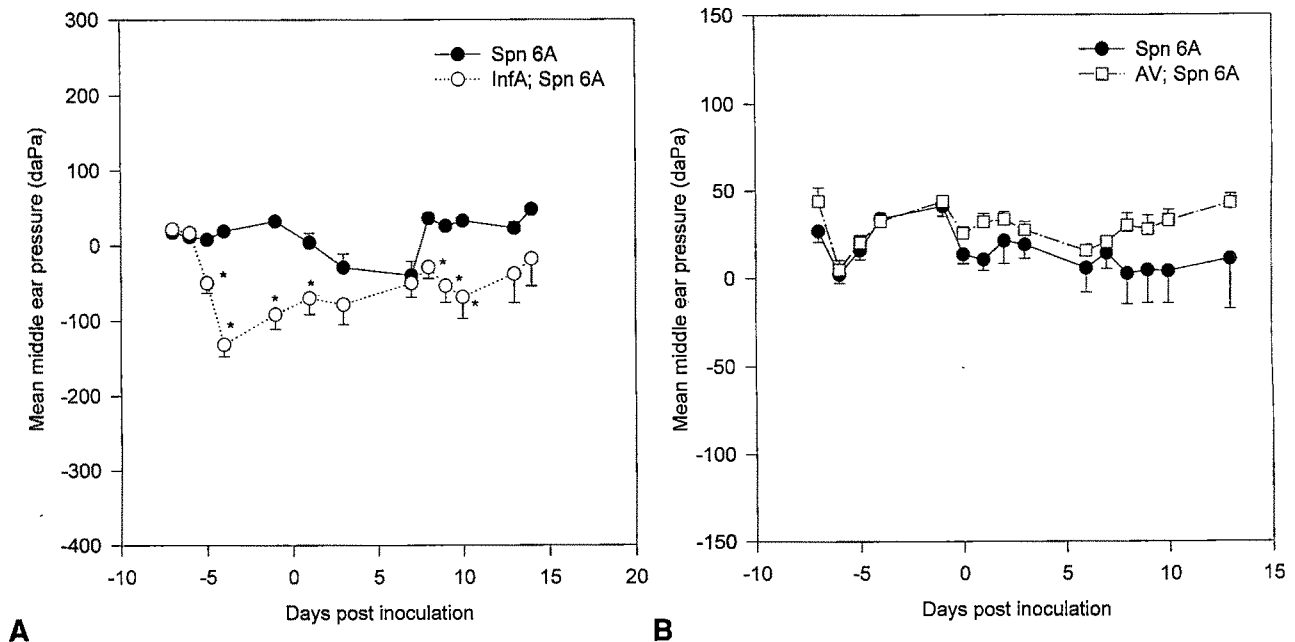


Fig 1. Comparison of mean middle ear pressure (MEP). Data shown represent arithmetic mean and SEM. Values below -60 daPa are considered abnormal for chinchilla.¹⁸ A) Between chinchillas inoculated intranasally with *Streptococcus pneumoniae* type 6A (Spn 6A) alone and those inoculated with Spn 6A in combination with influenza A virus (InfA) as determined by tympanometry over 21-day observation period. * — Statistically significant ($p < .01$). B) Between chinchillas inoculated intranasally with Spn 6A alone and those inoculated with Spn 6A in combination with adenovirus type 1 (AV) as determined by tympanometry over 21-day observation period.

Virus Culture. Adenovirus culture was performed by the Clinical Microbiology Laboratories at The Ohio State University Medical Center. A 0.35-mL aliquot of the nasal lavage fluid was added to an equal volume of viral transport medium and kept on ice. The aliquots were assessed for the presence of virus by characteristic CPE (cell rounding and degeneration) on A549 and normal human dermal fibroblast cells for up to 21 days. Positive identification was made with a fluorescein-tagged monoclonal antibody (Adenoclone; Cambridge Bioscience, Worcester, Mass). Because extensive, previously reported data from this laboratory have established a correlation of clinical signs during experimental OM in the chinchilla with the presence of influenza A virus, culture for influenza virus was not performed as part of the study.^{3,12,14}

Statistics. The Mann Whitney rank sum test was used in analysis of MEP, TM inflammation, and nasopharyngeal colonization between the control and virus groups. Two-way classification analysis of variance (χ^2 test) was used to analyze the effects of viral infection on Spn OM. A χ^2 analysis was used to analyze the association of Spn concentration of nasal lavage and positive culture of MEFs. Significance was accepted for all analyses when $p < .05$.

RESULTS

MEP. Chinchillas that received only Spn 6A demonstrated normal MEP (-39 to -48 daPa) during the

experimental study period. Influenza A virus induced a significant decline in MEP as early as 3 days after intranasal inoculation of the virus; it persisted for up to 10 days after intranasal inoculation of Spn 6A (-132 to -69 daPa, $p < .01$; Fig 1A¹⁸). In contrast, chinchillas with an antecedent adenovirus type 1 infection before challenge with Spn 6A did not exhibit decreased MEP (21 to 44 daPa; Fig 1B).

TM Inflammation. Chinchillas inoculated intranasally with only Spn 6A showed mild TM inflammation 3 days after challenge that persisted for up to 10 days (rating scale, 0.8 to 1.2). Influenza A virus inoculated alone induced significant TM inflammation by 6 days after inoculation. The TM inflammation persisted in the combined influenza A virus–Spn 6A–inoculated chinchillas compared to the control group for up to 10 days after challenge (rating scale, 1.8 to 2.7; $p < .01$; Fig 2A). There was no difference in TM inflammation evident in the adenovirus-inoculated chinchillas either before or after challenge with Spn 6A when compared to control chinchillas challenged only with Spn 6A (rating scale, 0.7 to 0.9; Fig 2B).

Nasopharyngeal Colonization. Influenza A virus infection of the nasopharynx resulted in a statistically significant increase in the concentration of Spn 6A as evidenced by a 2-log increase in CFU per milliliter of nasal lavage fluid by 24 hours after challenge (Fig 3A). The level of colonization in the combined influenza A virus–Spn 6A–infected group re-

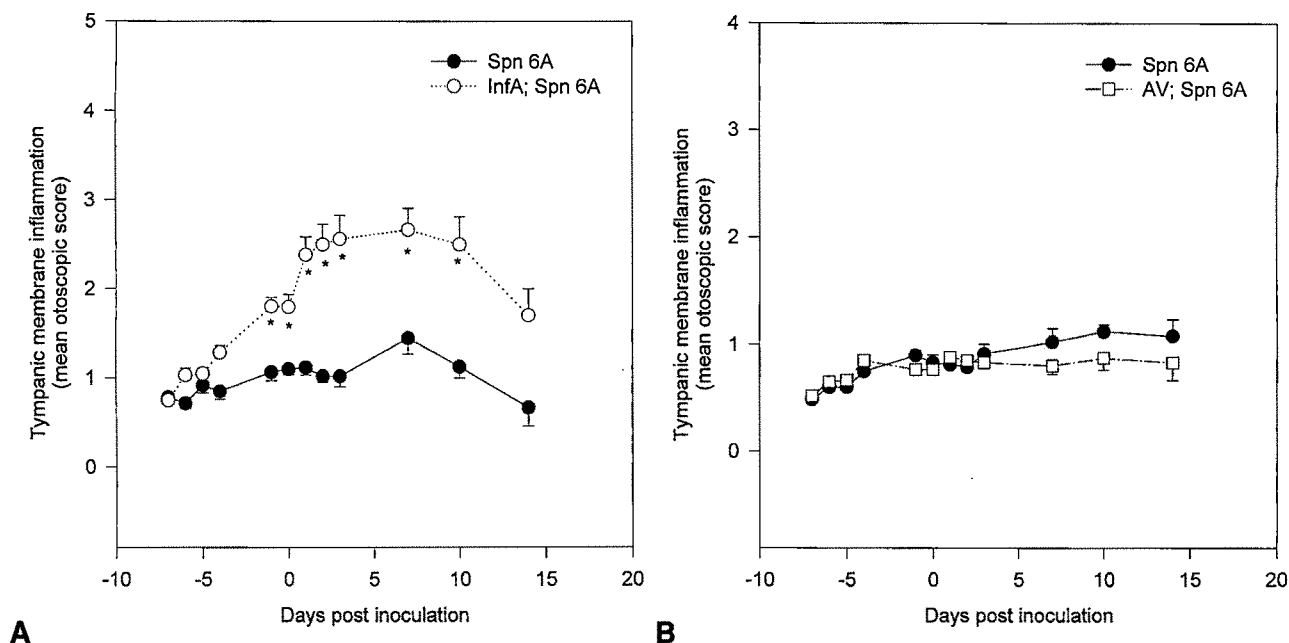


Fig 2. Comparison of mean tympanic membrane inflammation scores, obtained by means of otoscopy. Values shown represent arithmetic mean and SEM derived from minimum of 6 ears from 3 chinchillas rated on scale of 0 to 4+. A) Between chinchillas inoculated intranasally with Spn 6A alone and those inoculated with Spn 6A in combination with InfA. * — Statistically significant ($p < .01$). B) Between chinchillas inoculated intranasally with Spn 6A alone and those inoculated with Spn 6A in combination with AV.

maintained higher than that in the controls inoculated only with Spn 6A for the 14-day duration of the experiment. Adenovirus infection of the nasopharynx did not affect colonization with Spn 6A. The concentration of Spn 6A per milliliter of the nasal lavage fluid revealed no significant differences in ei-

ther the incidence or duration of colonization between adenovirus-infected and control chinchillas. The Spn 6A persisted in both cohorts during the 14-day observation period (Fig 3B). Adenovirus was isolated from lavage fluids for up to 7 days after Spn inoculation.

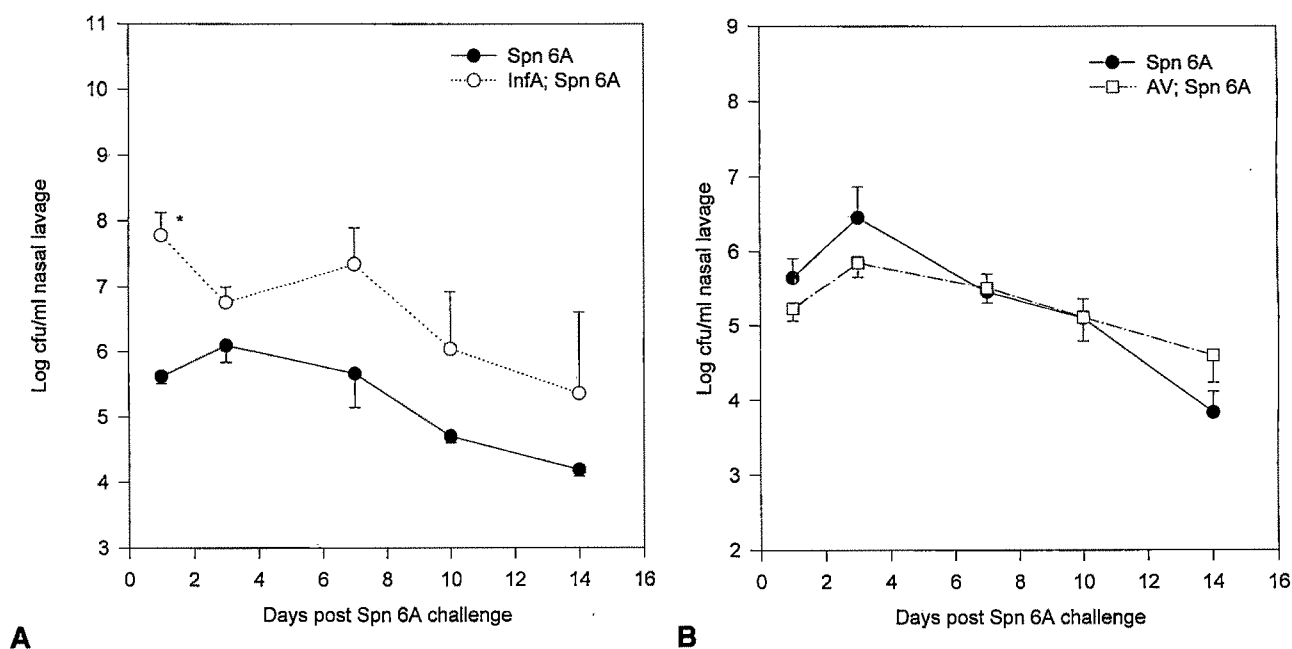


Fig 3. Nasopharyngeal colonization dynamics. Data represent mean number of colony-forming units of Spn 6A $\pm$ SEM per milliliter of nasal lavage fluid from 3 chinchillas. A) Comparison between chinchillas challenged intranasally with Spn 6A alone, and those that also had prior intranasal challenge with InfA given 7 days earlier. * — Statistically significant ($p < .05$). B) Comparison between chinchillas challenged intranasally with Spn 6A alone and those that also had prior intranasal challenge with AV given 7 days earlier.

CULTURE-POSITIVE PNEUMOCOCCAL OTITIS MEDIA INDUCED BY INTRANASAL CHALLENGE OF CHINCHILLAS WITH SPN TYPE 6A ALONE, OR IN COMBINATION WITH INF A OR AV ONE WEEK BEFORE SPN 6A CHALLENGE

Day	InfA + Spn 6A		Spn 6A ^a		AV + Spn 6A		Spn 6A ^b	
	Ear ^c	CFU/mL	Ear	CFU/mL	Ear	CFU/mL	Ear	CFU/mL
1	3R	9.9×10^2	18R	6.9×10^5	14R	1.0×10^2	1R	2.2×10^2
			18L	7.4×10^2	18L	3.1×10^3	1L	1.4×10^2
							3L	9.7×10^2
3	5L	1.0×10^2			8L	20		
	7R	4.8×10^5						
	7L	3.8×10^5						
7	11R	2.0×10^2	14R	1.2×10^3	22L	40	10R	1.2×10^3
	11L	5.4×10^3						
	13R	1.5×10^3						
	13L	9.1×10^3						
10	15L	1.2×10^2			30R	4.9×10^4	19R	7.9×10^2
	21R	1.5×10^4						
	21L	9.7×10^3						
	19R	5.2×10^4						
	19L	3.0×10^3						
14	26R	3.0×10^2					23R	3.8×10^2
	26L	7.0×10^2						

Total No. of

chinchillas (ears)

9 (15)^d

2 (3)

5 (5)

5 (6)

Spn — *Streptococcus pneumoniae*, InfA — influenza A virus, AV — adenovirus type 1, CFU — colony-forming units.^aControl group for InfA + Spn 6A—infected chinchillas.^bControl group for AV + Spn 6A—infected chinchillas.^cAnimal number and L for left ear or R for right ear. Specimens obtained from 6 ears, from 3 chinchillas, were cultured at each time period.^d $p < .05$ versus control group.

Invasion of ME and Induction of OM. The combination of an antecedent influenza A virus infection of the nasopharynx and intranasal inoculation with Spn 6A resulted in a statistically significant increase in the incidence of Spn 6A culture-positive OM: 9 of 15 chinchillas, compared to 2 of 15 chinchillas inoculated intranasally with Spn 6A only ($p < .05$; see Table). The incidence of OM peaked between 3 and 10 days after intranasal inoculation in the influenza A–Spn 6A combined inoculation cohort. Bilateral disease was induced in 14 of a possible 18 ears. There was an association between the level of Spn nasopharyngeal colonization and induction of culture-positive OM in the group with influenza virus before Spn nasal challenge. All 6 chinchillas with an Spn concentration of $>6 \times 10^6$ CFU/mL in the nasal lavage fluid developed culture-positive MEE, compared to 3 of 9 chinchillas with an Spn level of $<6 \times 10^6$ CFU/mL. A χ^2 analysis revealed a statistically significant association between the level of colonization of the nasopharynx and the incidence of OM ($p < .05$). The addition of an antecedent infection of the nasopharynx with adenovirus before intranasal inoculation with Spn 6A did not result in an increased incidence or duration of pneumococcal OM. Five of the 15 chinchillas developed OM both in the adenovirus–Spn 6A combined cohort and in the control cohort that

received Spn 6A without virus (see Table).

Adenovirus Culture of Lavage Fluids. Adenovirus type 1 was cultured from the nasal lavage fluid for up to 7 days after Spn 6A inoculation (total of 14 days after inoculation with adenovirus). It has been previously demonstrated that this strain of adenovirus induces an active upper respiratory tract infection in chinchillas, predisposes them to NTHi-induced OM, and is culturable from the chinchilla nasopharynx for up to 14 days after intranasal inoculation.^{6,7}

DISCUSSION

Viral potentiation of bacterial adherence and colonization is one of several proposed mechanisms that, acting together, can contribute significantly to OM pathogenesis.⁸ Intranasal challenge of chinchillas with both influenza A virus and Spn has been described by Giebink et al^{3,19} as resulting in an increased susceptibility to OM and was suggested to be related to the ability of the virus to induce negative MEP, polymorphonuclear leukocyte dysfunction, and alteration in the mucosal clearance of the Spn. These authors were the first to demonstrate an increased concentration of Spn in the nasal washings of chinchillas previously inoculated with influenza virus. Subsequent studies by Plotkowski et al² showed that in-

fluenza A virus enhances the adherence of Spn type 1 to mouse tracheal epithelium. The demonstrated nasal and otologic effects of experimental influenza A virus infection of healthy human adult volunteers, previously described by Doyle et al,²⁰ also support a causal role for this virus in the pathogenesis of OM, possibly due to the early development of eustachian tube dysfunction and abnormal MEP. More recently, that same group demonstrated that influenza A virus infection of adult volunteers promotes colonization of the oropharynx by Spn.²¹

Data from the present study expand these previous reports by indicating that the combined influenza A virus–Spn 6A infection, in addition to inducing a significant decline in MEP, and increased TM inflammation when compared to controls, also resulted in a predominantly bilateral invasion of the ME by Spn 6A. Our data provide, for the first time, an assessment of the bacterial load and persistence of Spn 6A in the ME after intranasal inoculation. Nasopharyngeal lavages, as well as MEF aspirates, provide a semiquantitative assessment of the concentration of the bacteria, and we have demonstrated a statistically significant relationship between the concentration of bacteria in the nasopharynx and the concentration of Spn 6A per milliliter of MEF. Moreover, it is readily apparent that prior intranasal inoculation with influenza virus promotes a sustained presence of Spn 6A at a relatively constant concentration of between 10^2 and 10^4 CFU/mL of MEF in chinchillas.

In contrast to the data obtained from the influenza A virus–infected group, results from the present study indicate that adenovirus type 1 does not act synergistically with Spn 6A with regard to enhancing either NP colonization or OM in the chinchilla. The adenovirus type 1 strain used in this study has been shown previously to interact synergistically with NTHi to promote enhanced colonization of the nasopharynx and OM in the chinchilla model.^{6,7} The course of the antecedent adenovirus infection, the MEP, and the TM inflammation observed during this study were comparable to those reported previously from adenovirus–NTHi synergy studies.^{6,7} Moreover, adenovirus was cultured from the nasopharyngeal lavage fluids for up to 7 days after Spn inoculation, indicating the presence of an active adenovirus infection at the time of intranasal challenge with Spn 6A. Our in vivo data are in contrast to those of previously published reports that indicate that adenovirus type 1 enhances the adherence of several Spn capsular types, including 6, to A549 cells in vitro.⁹ The most obvious reason for this difference may be the use of the lung carcinoma cell line versus the chinchilla model.

It is also not clear why infection with adenovirus

type 1 would act synergistically with NTHi in vivo⁷ and enhance adherence to A549 cells in vitro but not enhance Spn adherence in vivo. One possible explanation could be innate differences in the interactions of Spn and NTHi with the host respiratory tract mucosa.²² The NTHi cells attach to receptor epitopes in mucins, and adenovirus type 1 induces gross changes in the amount and viscosity of mucus secretion in the chinchilla, thereby possibly promoting enhanced colonization by NTHi.⁷ In contrast, Spn cells do not bind to purified mucins,⁹ and therefore, adenovirus-induced increased mucus production may not impact on Spn adherence and colonization via this mechanism. It is important to note that the inability to demonstrate a synergistic interaction between adenovirus type 1 and OM bacterial pathogens is not limited to Spn. Adenovirus type 1 also does not act synergistically with *Moraxella (Branhamella) catarrhalis* to induce OM in the chinchilla.²³

It cannot be determined with certainty from the present study the exact mechanism whereby influenza A virus promotes enhanced colonization of the chinchilla nasopharynx and invasion of the ME by Spn. Giebink and Wright¹⁹ originally postulated that influenza virus infection of the chinchilla eustachian tube may result in an increased exposure of Spn receptor sites. Influenza A virus is known to promote attachment of other bacterial pathogens to viral glycoproteins, or actual virus particles budding from infected cells.^{24,25} Moreover, influenza A virus–induced inflammation may promote the induction of platelet activating factor receptors, which were described by Cundell et al.²⁶ Recent data from our laboratory suggest that the antecedent influenza A virus preferentially selects for the more virulent opaque phenotype of Spn 6A (Tong et al, unpublished observations).

Plotkowski et al² have shown that Spn appears to preferentially bind to differentiating cells during epithelial regeneration subsequent to influenza A virus–induced damage; this finding suggests that the repertoire of receptors for microbial adhesins may also vary after influenza virus–induced injury. These same authors propose that influenza virus neuraminidase may also remove sialic acid residues in oligosaccharide side chains of membrane glycoproteins and unmask cellular receptors for pneumococcal adhesins. Lectin-histochemical data from our laboratory, however, indicate that the strain of influenza A virus used in this study does not remove the sialic acid residues from membrane glycoproteins in the chinchilla eustachian tube and ME (DeMaria, unpublished observations), presumably because the viral neuraminidase is specific for sialic acid residues linked to α 2-3 Gal

or α 2-6 Gal, whereas the lining of the chinchilla tubotympanum contains sialic acid linked primarily to β 1-3 Gal or β 1-4 Gal.

In conclusion, the results of the present study indi-

cate that the effect of an upper respiratory tract virus infection on the colonization of the nasopharynx and invasion of the ME during experimental Spn OM in the chinchilla may vary significantly, depending on the virus involved.

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MASTOID PNEUMATIZATION OF THE PATULOUS EUSTACHIAN TUBE

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The pathophysiology of the patulous eustachian tube (PET) remains unclear. The degree of mastoid cell pneumatization is considered an indicator of chronic inflammation of the middle ear. We used the mastoid cell area to investigate the relationship between past chronic inflammation of the middle ear cavity and a PET in 84 patients (20 to 83 years old). The mastoid cell size was calculated from radiographs and analyzed relative to the history of otitis media (OM). The controls were 100 normal ears. The patients' mastoid cell size was significantly suppressed versus that of the controls, in both 31 PET cases with and 53 PET cases without past OM. We surmise the possibility that the PET ears had experienced inflammation even when the patients had no history of OM and the tympanic membrane showed no OM sequelae. This study indicates the existence of some relationship between a history of chronic inflammation of the middle ear cavity and a PET.

KEY WORDS — chronic inflammation, mastoid pneumatization, otitis media, patulous eustachian tube, rectangular area method.

INTRODUCTION

Many aspects of the origin and pathophysiology of the patulous eustachian tube (PET) remain to be elucidated. However, it has been speculated that a decrease in body weight and pregnancy are among the causative factors that lead to the manifestation and aggravation of a PET. On the other hand, it has been pointed out that in children there is a relationship between otitis media with effusion (OME) and a eustachian tube (ET) with a low opening pressure, that is, a so-called compliant tube.¹ It has been reported that even when tympanic tube insertion is performed for cases of OME with a compliant tube, the prognosis is poor in about half of the cases after removal of the tympanic tube.² In patients with a PET, the opening pressure for the ET is extremely low, and a relationship to a compliant tube can also be surmised. In the past, we carried out an investigation of the morphological features of the pharyngeal orifice of the ET in cases with a PET, and endoscopic observation of the patient group with no history of otitis media (OM) revealed that the lumen of the pharyngeal orifice of the ET was patent.³ The findings in these patients were thus consistent with the typical findings of a patent pharyngeal orifice in which Rosenmüller's fossa is enlarged. On the other hand, the patient group with a history of OM did not yield such typical findings of a patent pharyngeal orifice. We thus surmised that the cases broadly classified under the simple diagnosis of a PET have the potential to show different disorders on the basis of whether there has been a history of OM.

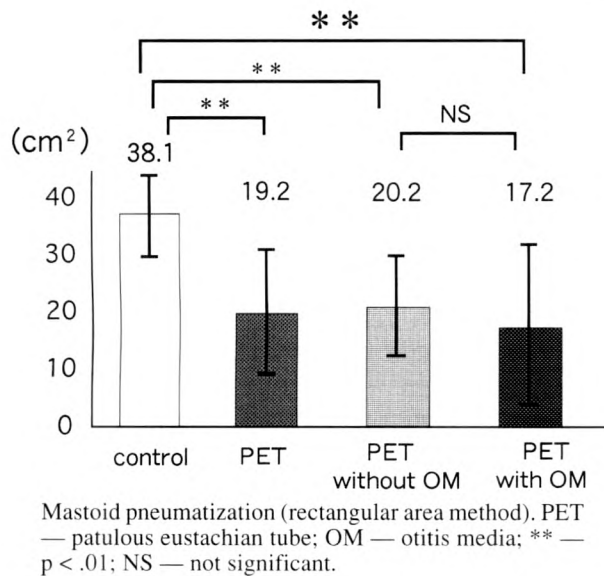
It is a well-known fact that mastoid pneumatization is inhibited during infancy when there is stimulation due to inflammation, such as that in cases of OM.⁴⁻⁶ For this reason, the degree of pneumatization of the mastoid cells can be used as an indicator of a history of chronic inflammation of the middle ear.^{7,8} Thus, if PET cases include cases both with and without a history of OM, it can be surmised that — because of the absence of past stimulation due to inflammation — pneumatization of the mastoid cells will be better in the cases without a history of OM than in the cases with a history of OM. But we cannot surmise that pneumatization of the mastoid cells will be better in cases without a history of OM than in a control group. Accordingly, we used radiographic films to investigate the degree of pneumatization of the mastoid cells in patients with a PET, with the cases divided on the basis of the presence or absence of a history of OM. With this study design, we investigated whether there was any correlation between a PET and a history of OM.

MATERIALS AND METHODS

The subjects of this study were 84 patients, ranging in age from 20 to 83 years (mean age, 53 years). They had been found to have a PET at the Outpatient Clinic of the Department of Otorhinolaryngology, Jikei University School of Medicine, Tokyo, or the Department of Otorhinolaryngology, Jikei University School of Medicine, Aoto Hospital, during the period from July 1997 through April 1998. The gender composition was 18 men and 66 women. X-ray pho-

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tographs were taken for each of these patients, and each also underwent pure tone audiometry and a detailed examination of the tympanic membrane. In addition, X-ray photographs of the ear were taken by Schüller's projection, and the rectangular area method⁹ was used to calculate the size (area) of the mastoid cells. Thirty-five of the patients were determined to have bilateral PETs, and they were included in the study on the basis of the determination of the size of the mastoid cells only on the more symptomatically severe side.

For each patient, the characteristics of the condition of the PET were ascertained by questioning the patient regarding the existence of subjective symptoms such as a feeling of fullness of the ear, autophony, or tinnitus. A detailed inquiry was also made regarding the presence or absence of a history of OM, and further evaluation was carried out by means of the 4 examination methods listed below. (Only patients who complained of symptoms caused by a patulous state of the ET were classified as having a PET. Patients who simply had a patulous state of the ET but did not complain of any subjective symptoms attributable to that state were excluded.)

1. *Findings for dynamic movement of the tympanic membrane.*^{10,11} With a fiberscope, momentary retraction of the tympanic membrane is seen when Toynbee's test is carried out, together with subsequent recovery, and/or respiratory fluctuation of the tympanic membrane is seen during deep breathing.

2. *Sonotubometry.*¹² When sonotubometry is performed, there is prolongation of the duration of tube opening, or there is fluctuation of the baseline indicative of closing failure.

3. *Otoscopy.* With an otoscope, the sound of the patient's breathing or voice can be heard. Patients

put one side of the otoscope into their external ear canal, and we put the other side of the otoscope into our external ear canal. We assess the patient's nose breathing or voice through the otoscope.

4. *Therapeutic diagnosis.* When a cotton swab soaked in lidocaine hydrochloride is inserted into the pharyngeal orifice of the ET and the ET is closed, the patient experiences alleviation or disappearance of the subjective symptoms.

Not all patients with a PET will show a positive result for each of these examinations. In this study, if the cases fulfilled at least 2 of these criteria, we regarded them as PET cases.

In addition, each of the patients with a PET was interviewed in detail, and the condition of the tympanic membrane was observed. On the basis of the overall findings, the patients were classified into one of the following groups: 1) an OM-positive group, who had a specific history of treatment for OM during infancy and in whom the tympanic membrane showed sequelae of OM such as thinning or calcification; and 2) an OM-negative group, who had no history of OM and in whom the tympanic membrane appeared normal.

As the normal controls for this study, a total of 100 ears of 50 healthy adult volunteers were used. The age range was from 17 to 78 years (mean age, 49 years). The gender composition was 26 men and 24 women. We confirmed that these control group ears were normal in terms of the visual examination of the tympanic membrane and the pure tone audiometry test. Informed consent was obtained from each subject in accordance with the principles of the Declaration of Helsinki. Then, X-ray photographs of the ears were taken by Schüller's projection, and the rectangular area method was used to calculate the size (area) of the mastoid cells, in the same manner as for the PET patients.

RESULTS

Of the total of 84 ears with a PET that were investigated in this study, 31 ears (36.9%) were classified into the OM-positive group, and the remaining 53 ears (63.1%) were classified into the OM-negative group.

The data for the mean area of the mastoid cells in each of the experimental groups are presented as bar graphs in the Figure. It is seen that the mean mastoid cell area for the total 84 ears with a PET was 19.2 cm². This was significantly smaller than the mean area of 38.1 cm² determined for the mastoid cells of the 100 control group ears (Student's *t*-test, $p < .01$).

The mean mastoid cell area for the 31 PET ears in the OM-positive group was 17.2 cm², which was also significantly smaller than the mean area in the control group (Student's *t*-test, *p* < .01). The 53 PET ears in the OM-negative group showed a mean mastoid cell area of 20.2 cm², and even this value was also significantly smaller than the mean area in the control group (Student's *t*-test, *p* < .01). The mean mastoid cell area was smaller in the OM-positive group than in the OM-negative group, but not significantly.

The mean mastoid cell area for the 18 male PET ears was 18.2 cm², and the mean area for the 66 female PET ears was 19.5 cm². There was thus no statistically significant difference in the mean mastoid cell area between the sexes in the PET ears. The mean mastoid cell area for the 52 male control ears was 39.2 cm², and the mean area for the 48 female control ears was 37.0 cm². There was thus also no statistically significant difference in the mean mastoid cell area between the sexes in the control ears.

In 49 of the patients with a PET, this condition was found to be unilateral. The mean mastoid cell area of the contralateral healthy ears of these patients was compared with the control group data. The mean value for the mastoid cell area of the healthy ears in these cases with a unilateral PET was determined to be 19.7 cm², and this value was significantly smaller than the mean value of 38.1 cm² for the mastoid cells of the control group ears (Student's *t*-test, *p* < .01).

DISCUSSION

The pathological condition of a PET was first reported in 1864 by Schwarze.¹³ Since then, numerous reports have dealt with this condition, but its origin and pathophysiology have still not been fully elucidated. On the other hand, it has been reported that ET closing failure is involved as a causative factor in such diseases as retraction cholesteatoma, adhesive middle ear lesions, and OME.^{14,15} Nevertheless, the relationship of a PET to those diseases has not yet been completely clarified.

As a technique for diagnosing a PET, the method of testing by sonotubometry reported by Virtanen¹² is well known. However, even when this test does not reveal any clear prolongation of the duration of tube opening or fluctuation in the baseline, there are patients in whom a PET is suspected on the basis of the results of a detailed interview. In particular, a PET is strongly suspected at the time of examination if the patient's symptoms are alleviated by bending the upper body forward so that it nearly touches the knees, and if the symptoms disappear when the patient lies down. In our department, as an aid to diagnosing

whether the ET is open or closed, we use a magnifying otoscope or a fiberscope to observe the dynamic movement of the tympanic membrane at the time of performance of Toynbee's test or Valsalva's maneuver.¹⁰ Careful observation of the dynamic movement of the tympanic membrane permits accurate determination of whether the ET is open or closed. In patients with a PET that is always open, fluctuation of the tympanic membrane can be confirmed at the time of breathing. In the case of patients with a semipatulous ET or a relative closing failure of the ET, the tympanic membrane shows transient retraction at the time of performance of Toynbee's test, and it is then possible to observe the manner in which the membrane returns instantly to its normal position. In addition, other effective means of achieving a diagnosis of a PET are examination with an otoscope and therapeutic diagnosis (alleviation of the symptoms by cotton swab insertion into the pharyngeal orifice of the ET).

Of the total of 84 ears with a PET that were investigated in this study, we found that 36.9% of the ears had a history of repeated OM or showed evidence of sequelae of OM such as calcification or thinning of the tympanic membrane when the membrane was visually inspected. This percentage of such ears is relatively high. However, it can be surmised that there are patients who have forgotten that they had OM during childhood, or in whom there were few objective symptoms because the inflammation was mild in severity, or in whom there are no sequelae involving the tympanic membrane. In this light, there is a strong possibility that the true incidence of a history of OM in patients with a PET is actually higher than the incidence we determined in this study.

It is generally known that the development (ie, size) of the mastoid cells during childhood is inhibited in the event that there is exposure to chronic inflammation of the middle ear cavity. Accordingly, it is possible to surmise a history of OM and the severity thereof on the basis of the size of the mastoid cells.⁴⁻⁸ To accomplish this, we investigated the state of development of the mastoid cells in our patients by means of radiographs. Imai et al⁹ determined the area of the mastoid cells by applying the rectangular area method to radiographs of the ear obtained by Schüller's projection. Others reported finding a good correlation between the mastoid cell area determined with a planimeter and the mastoid cell area determined by the rectangular area method.^{16,17} On the basis of those results, we decided to use the rectangular area method to determine the mastoid cell area in our present patient series.

The mean size of the mastoid cells in the 84 ears

with a PET was found to be significantly smaller than the mean size determined for the control group. However, even in the OM-negative group, the mean size of the mastoid cells was significantly smaller than the mean size in the control group. On the basis of these findings, it can be surmised that even in patients with a PET but no definitely confirmable history of OM, the mastoid cells had been exposed to inflammatory stimulation at some time in the past. In consideration of the fact that the pathophysiology of the PET is the opposite of that of ET stenosis, we had expected that the development of the mastoid cells would be nearly the same as that in normal ears. However, our findings in this study clearly demonstrate that the size of the mastoid cells in the PET is actually smaller than normal. In terms of mastoid pneumatization, there was no difference between the PET cases with and without a history of OM.

In addition, we found no gender-based difference in the area of the mastoid cells in the PET. We also found no gender-based difference in the area of the mastoid cells in the control group. So, we can ignore any difference in the size of the mastoid cells between the sexes.

We also compared the size of the mastoid cells of the normal ET in 49 patients who had a unilateral PET with the size in the control group. The data revealed that even in the normal ear of the patients, the mastoid cell size was significantly smaller than the control size determined in the healthy volunteers.

We think that the most interesting finding of this study is the fact that even in ears with a PET but with no history of OM and no evidence of sequelae of OM, the size of the mastoid cells was smaller than in the control group ears. This indicates that OM had indeed occurred in the past. Accordingly, it can be surmised that cases of a PET that are thought to have no history of OM actually experienced mild inflammation in the past that did not leave any scarring, calcification, or thinning of the tympanic membrane, and that the patient experienced few subjective symptoms or later forgot about them.

Overall, these various findings indicate that there is some kind of close involvement between the PET and OM occurring in childhood. Therefore, we next consider the question of which of these 2 disorders is the cause and which is the effect.

First, let us hypothesize that the patulous state of the ET is the cause of OM. It is said that in general, the ET of children is in a patent state.¹⁸ However, in patients who later exhibit a PET, there is the possibility that this development of an abnormal patency of the ET as an adult is a result of a congenital disposition or that it was latent from the time of childhood. Such patients who later exhibit a PET are also at increased risk of infections of the middle ear during childhood in comparison with normal children. Infections result in exposure of the middle ear cavity to an inflammatory stimulus over a long period of time, and this can be postulated to cause suppression of the growth of the mastoid cells. This concept supports various published reports that claim that ET closing failure is the cause of middle ear lesions.^{14,15}

The contrary hypothesis is that the OM is the cause of the state of abnormal patency of the ET. It can be postulated that long-term exposure of the middle ear or the ET to a state of inflammation leads to loss of elasticity of the ET mucosa, a decrease in the number of goblet cells in the ET mucosa, and atrophy of the ET muscle, culminating in an abnormal state of patency of the ET. In the clinic, development of a PET is sometimes seen to follow OM, and thus it is impossible to rule out completely this latter hypothesis, that OM is the cause of the state of abnormal patency of the ET.

In fact, the concepts presented above in support of each of these hypotheses are mere speculation, in light of the fact that there have been no reports of detailed pathological studies of the ET in cases of a PET. Therefore, further observations and investigations of the state of the middle ear and the ET during childhood and adolescence must be carried out to elucidate the true cause-and-effect relationship between OM and abnormal patency of the ET.

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RETROGRADE MASTOIDECTOMY WITH CANAL WALL RECONSTRUCTION: A SINGLE-STAGE TECHNIQUE FOR CHOLESTEATOMA REMOVAL

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The goal of this retrospective study was to report the preliminary results of the retrograde mastoidectomy technique with canal wall reconstruction used as a primary treatment method for cholesteatoma. This synthesis of canal wall up (CWU) and canal wall down (CWD) techniques was performed in 70 patients (75 ears; 35 pediatric, 40 adult) with an average 45-month follow-up. Surgical intervention involved removal of a portion of the canal wall for exposure and extirpation of the cholesteatoma, followed by reestablishment of the canal wall during reconstruction in a single stage. This leaves the mucosa relatively undisturbed and limits the extent of canal wall removal, facilitating mastoid aeration and preservation of anatomy. Recurrent disease occurred in 5% of cases. The hearing improvement was statistically significant ($p < .05$), with an average preoperative 4-frequency pure tone average air-bone gap of 27.2 dB improving to 11.5 dB. No patient had a worsening of hearing. The surgery takes less time than traditional techniques, is reproducible and easily taught, and can be universally applied to all cholesteatoma patients as primary treatment.

KEY WORDS — canal wall reconstruction, cholesteatoma, ossicular reconstruction, retrograde mastoidectomy.

INTRODUCTION

Surgical management of cholesteatoma remains controversial, with the main argument centering around the surgical handling of the posterior canal wall. The canal wall up (CWU) procedure preserves the normal anatomy of the ear canal, thus avoiding the risk of bowl problems and the necessity for periodic cleaning. The healing time is reduced, and hearing results may be better. However, a fairly high cholesteatoma recurrence rate (20% to 40%) is a major limitation of this technique,^{1,2} and second-look procedures at 1 year after surgery are often required.³ In addition, exposure of the epitympanum can be very difficult, leading to blind and piecemeal removal of the cholesteatoma in this area, which contributes to the high residual rate.

The canal wall down (CWD) technique creates an open cavity after removal of the bony posterior canal wall. This widely exposes the epitympanum and mastoid, facilitating complete removal of the cholesteatoma sac and lowering the recurrence rate to 5% to 10%.^{4,5} The main disadvantages of this technique are related to the necessity for periodic cleaning of the mastoid cavity. Subsequent bowl infections can occur, especially when the cavity becomes wet, causing significant lifestyle changes, particularly in the pediatric age group.⁴

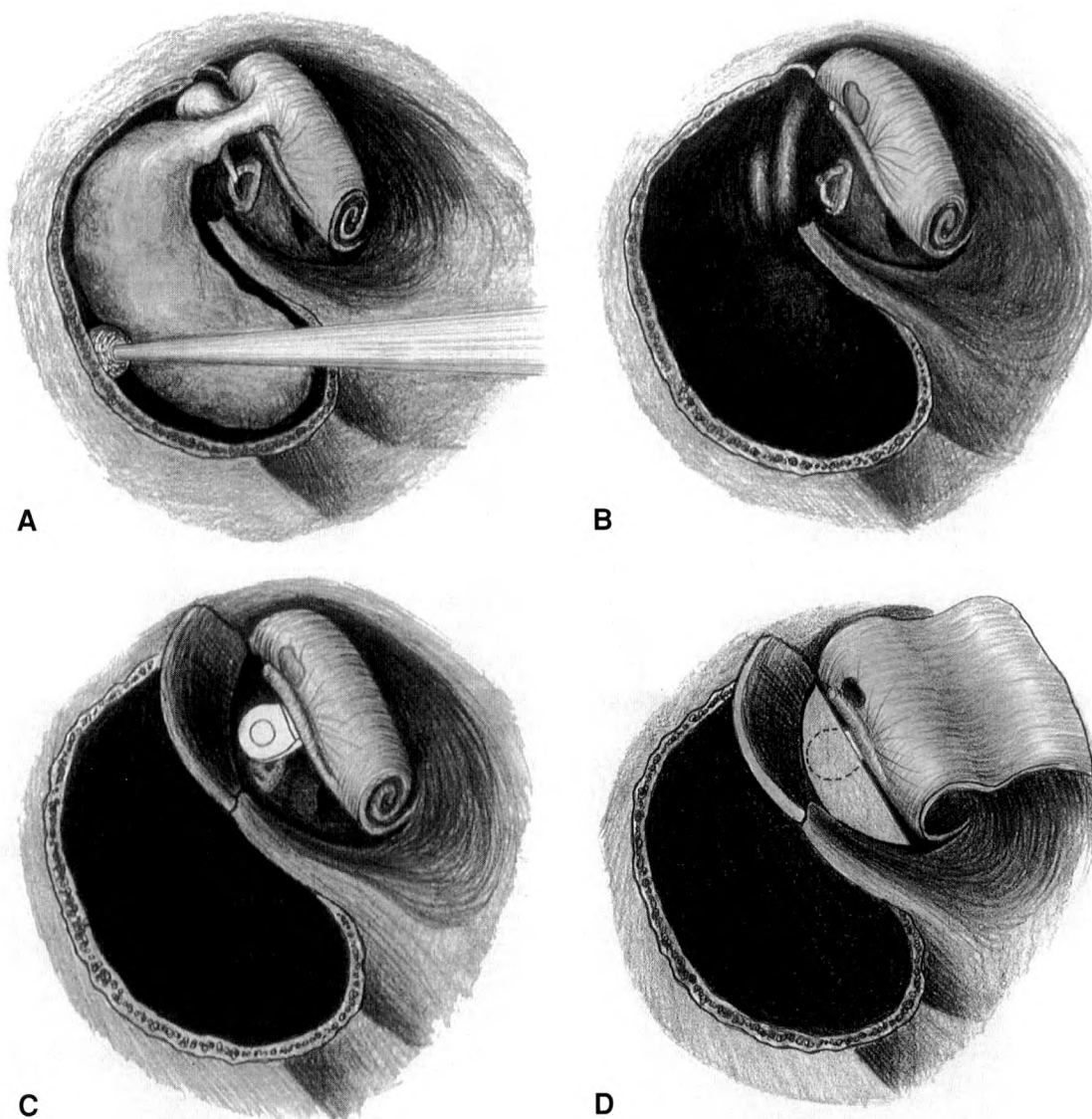
Canal wall reconstruction has been primarily used in the past as a second-stage technique following tra-

ditional CWD procedures. In this situation, an attempt at canal wall reconstruction is performed in order to rehabilitate a previously performed CWD surgery. Because of the severe extent of mucosal disruption in the mastoid, as well as the extent of reconstruction necessary in these cases, the results have been less than optimal. However, removal and subsequent reestablishment of the canal wall in *primary* cholesteatoma surgery is beginning to be reexamined, and this is what I am describing with the current study.

The retrograde mastoidectomy for cholesteatoma removal is a technique that combines the best of the CWU and CWD procedures with reconstruction in a single-stage operation in most cases. This approach involves following the cholesteatoma sac from its origin in the epitympanum into the mastoid, removing only enough bone to completely expose and remove the sac in a retrograde fashion. The canal wall and ossicular chain are reconstructed at a single sitting (Prof Jan Helms, University of Würzburg, Würzburg, Germany, personal communication, 1993). Although the concept of extended atticotomy, as well as following the cholesteatoma back from the external canal to create a small cavity, has been discussed in the past for limited disease,⁶ the combination of these techniques with canal wall reconstruction as a primary treatment method for all cholesteatomas has, to my knowledge, not been reported in an extensive series of patients. I describe here the results of using

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Schematic rendering of technique. A) View of cholesteatoma sac after bone removal. Diamond bur is used to expose sac. B) View of resected area; incus and head of malleus have been removed. C) Prosthesis insertion and reconstruction of posterior canal wall with cartilage from cyma. D) Reconstruction of posterior half of tympanic membrane by placement of cartilage on top of prosthesis.

the retrograde mastoidectomy for cholesteatoma removal in a consecutive series of 75 ears, with an average 45-month follow-up.

MATERIALS AND METHODS

TECHNIQUE

Cholesteatoma Removal. The mastoid cortex is widely exposed through a postauricular skin incision. A tympanomeatal flap is then developed, and the middle ear is entered inferiorly, away from the cholesteatoma, in order to determine the extent of disease in the middle ear. At this point, the incudostapedial joint is disarticulated to avoid trauma to the inner ear from the subsequent drilling. A canaloplasty is performed with a large conical bur, and the neck of the chole-

steatoma sac is visualized through its defect in the scutum. The conical bur is used to follow the cholesteatoma sac posteriorly (see Figure, A). It is essential that the cutting bur does not make contact with the cholesteatoma sac but, instead, leaves a thin layer of bone that is later removed with the diamond bur. The superior extent of the drilling must extend all the way to the tegmen and anteriorly to the head of the malleus, so that the epitympanum is completely exposed. This is similar to an atticotomy, but with more extensive bone removal.

The sac is followed back as posteriorly as necessary until a normal air cell or cholesterol granuloma is encountered behind the sac. This technique differs from that described by Tos,⁶ in which a small cavity

is created in case extensive cholesteatoma is encountered. Instead, I follow the sac toward the mastoid tip — a maneuver referred to as “turning the corner” — leaving the lower two thirds of the canal wall intact to facilitate reconstruction. This modification allows the removal of extensive cholesteatoma in a well-aerated mastoid, as frequently found in children, thus avoiding a CWD situation. The diamond bur is then used to remove the thin bone over the cholesteatoma sac, with extreme care taken not to violate the sac. The posterior edge of the sac is then identified, and this is dissected upward out of the mastoid cavity in a posterior-to-anterior direction. This maneuver allows visualization of any fistula of the bony labyrinth (horizontal semicircular canal). When the mastoid portion of the cholesteatoma has been dissected free, the incus is removed, and the head of the malleus is removed to complete the exposure. At this point, the sac remains intact, and its neck, entering the retraction in the tympanic membrane, can be visualized and resected from this area, leaving a small defect in the tympanic membrane (see Figure, B).

Reconstruction. Although removal of the cholesteatoma is important in reducing residual disease, reconstruction is equally important in preventing recurrence of retraction pockets. Primary ossicular reconstruction is performed in all ears, because the prosthesis acts as a scaffolding to support the cartilage reconstruction of the tympanic membrane and maintain the middle ear space during the healing phase.

To reconstruct the canal wall, a small diamond bur is used to form grooves in the bone at the tegmen superiorly and in the inferior canal wall. A piece of cartilage is harvested from the cyma of the conchal bowl to reconstruct the posterior canal wall. Because of its appropriate curvature, cartilage from the cyma is ideal for this purpose. It is essential that a good fit between the cartilage and the residual bony canal wall is achieved and that the superior edge of the cartilage reconstruction is placed medially so that it closely approximates the handle of the malleus (see Figure, C).

At the University of Arkansas for Medical Sciences (UAMS), the ossicular chain is reconstructed with a Dornhoffer-HAPEX partial ossicular replacement prosthesis (PORP) or total ossicular replacement prosthesis (TORP). This prosthesis is composed of a dense hydroxyapatite head, which is notched to facilitate its placement under the handle of the malleus.⁷ A cannulated shaft made out of HAPEX fits over the stapes capitulum and can be cut to size with a scalpel after appropriate measurements are taken (see Figure, C). The malleable link allows the head

to be tilted to accommodate the conical shape of the normal tympanic membrane. After the prosthesis is placed over the head of the stapes and under the neck of the malleus, a semicircular piece of cartilage is laid on top of it to reconstruct the posterior half of the tympanic membrane (see Figure, D).

In earlier surgeries that used the retrograde mastoidectomy, a space was left between the cartilage of the tympanic membrane and the canal wall. Although it was thought that this space would facilitate sound transmission, it led to some recurrent retractions in this area. Therefore, in order to prevent the recurrence of retraction pockets, good contact must be established between the tympanic membrane reconstruction and the cartilage reconstruction of the canal wall. Frequently, if a good approximation between the cartilages of the tympanic membrane and the canal wall reconstruction is not achieved, small pieces or slivers of cartilage can be added by the palisade technique. This has yielded good results without imparting a significant hearing loss. The reconstruction is then reinforced with a piece of perichondrium harvested from the conchal bowl, inserted in an underlay fashion, with a tympanomeatal flap placed on top of the canal wall reconstruction.

The canal is packed with antibiotic ointment, followed by a roll of Gelfoam in the external canal. The packing is removed 10 days after surgery, and the patient is instructed to perform the Valsalva maneuver 3 times a day, starting 2 weeks after the surgery. The Otovent has been used in children who are unable to perform this maneuver. The first postoperative audiogram is obtained 6 to 8 weeks after operation. If the patient is unable to perform the Valsalva maneuver or if the postoperative period is complicated by an effusion or retraction of the reconstructed tympanic membrane, a ventilation tube is placed 3 to 4 months after the surgery. Primary ventilation tube insertion is generally avoided. For the most part, the retrograde mastoidectomy allows removal of the cholesteatoma sac in one piece with direct exposure, so second-look surgery is only performed in those cases in which the cholesteatoma sac was violated and had to be removed piecemeal. The area of the sinus tympani is the most problematic region, as exposure here is difficult even with the retrograde mastoidectomy.

DATA COLLECTION AND ANALYSIS

A computerized otologic database was used to identify all patients who underwent surgical removal of cholesteatoma by the retrograde mastoidectomy between July 1994 and July 1997, with at least a 24-month follow-up. The surgeries were performed by the author or supervised residents at UAMS or Ar-

TABLE 1. CHANGE IN AIR-BONE GAP

	<i>Pediatric Cases (N = 35)</i>	<i>Adult Cases (N = 40)</i>	<i>All Cases (N = 75)</i>
Preoperative (dB)	30.7 ± 10.2	24.1 ± 9.9	27.2 ± 10.4
Postoperative (dB)	11.4 ± 6.6*	11.6 ± 4.2*	11.5 ± 5.4*
Data are mean ± SD.			
*p < .05.			

kansas Children's Hospital, Little Rock, Arkansas. A retrospective chart review extracted the following information: age, sex, preoperative audiogram, type of ossicular reconstruction, complications, postoperative audiogram, and surgical result with regard to recurrent and residual cholesteatoma, perforation, or effusion. The audiometric data are presented as a pure tone average air-bone gap (PTA-ABG) calculated for 500 Hz, 1,000 Hz, 2,000 Hz, and 3,000 Hz.⁸ A statistical comparison between the preoperative and postoperative hearing results was performed with the Student's *t*-test.

RESULTS

PATIENT POPULATION

During the study period, a total of 79 patients, representing 88 operated ears, were identified in whom the retrograde mastoidectomy was used for surgical management of cholesteatoma. Of these, 9 patients were excluded for the following reasons: 5 patients (7 ears) were lost to follow-up, 3 patients (4 ears) had either no postoperative audiogram or inadequate documentation of bone thresholds, and 1 patient (2 ears) had a lack of preoperative data. This left a total of 70 patients (40 male, 30 female), representing 75 ears, available for analysis. Of these, 32 were pediatric patients (35 ears) and 38 were 18 years of age or older (40 ears; average age, 29.3 years; range, 6 to 73 years). The average follow-up was 45 months (range, 24 to 60 months).

AUDIOMETRIC FINDINGS

Table 1 lists the audiometric findings. The average PTA-ABG for the pediatric cases improved from a preoperative value (±SD) of 30.7 ± 10.2 dB to a postoperative value of 11.4 ± 6.6 dB. Similarly, the average PTA-ABG for the adult cases changed from a preoperative value of 24.1 ± 9.9 dB to a postopera-

tive value of 11.6 ± 4.2 dB (overall average, 27.2 ± 10.4 dB, improving to 11.5 ± 5.4 dB). This improvement in hearing was statistically significant in both age groups (*p* < .05), but there was no statistically significant difference in the results between the pediatric and adult groups. A breakdown of hearing results is shown in Table 2.

Ossicular reconstruction was performed with a PORP in 43 ears, which showed an average postoperative PTA-ABG of 10.9 ± 4.8 dB. A TORP was used in 32 ears, which had an average postoperative PTA-ABG of 12.4 ± 6.1 dB. This difference was not statistically significant. No patient experienced a worsening of hearing as a result of surgery, but 3 patients had little or no improvement in their hearing after surgery.

CHOLESTEATOMA RECURRENCE

Recurrent cholesteatomas that required revision surgery were seen in 4 ears (2 adult and 2 pediatric, representing 5% of the total ears), and stable retraction pockets formed in an additional 2 ears (1 adult and 1 pediatric, or 3%). The recurrent disease was seen in the posterior superior tympanic membrane in 3 cases, all of which represented early cases in the series, before the posterior half of the eardrum was reconstructed with cartilage in tight approximation to the canal wall cartilage. The other recurrence was seen in a patient who was lost to follow-up for 2 years and then returned with an atelectatic eardrum in which the canal wall reconstruction had pulled back into the mastoid, similar to a spontaneous Bondy mastoidectomy. Although this patient's ear is not collecting debris and is actually dry, revision surgery is planned because of poor hearing. Other than this patient, canal reconstruction was successful in all cases (74 ears or 99%).

Pressure-equalizing tube insertion was performed 3 to 6 months after surgery in 9 ears (12%) for persistent effusion in Valsalva-negative individuals. A perforation was seen in 1 ear (1%) out of the entire series. Second-look surgery was performed in 5 ears (7%), and of these, no residual cholesteatoma was found in 4 cases; however, in the fifth case, known cholesteatoma had been left after the initial surgery,

TABLE 2. HEARING RESULTS

Air-Bone Gap	All Cases (N = 75)				Pediatric Cases (N = 35)				Adult Cases (N = 40)			
	Preop		Postop		Preop		Postop		Preop		Postop	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-10 dB (excellent)	5	7	34	45	1	3	18	51	4	10	16	40
11-20 dB (good)	15	20	35	47	5	14	12	34	9	23	23	58
21-30 dB (fair)	28	37	6	8	10	29	5	14	18	45	1	3
>30 dB (poor)	27	36	0	0	19	54	0	0	9	23	0	0

as it was positioned over a 1-mm fistula in the footplate of the stapes. Second-look surgery 9 months later revealed a small cholesteatoma pearl. This was removed, the small fistula was patched with perichondrium, and ossicular reconstruction was performed with a TORP, yielding a good hearing result.

Complications as a direct result of surgery were rare. Bony fistulae of the horizontal semicircular canal were seen in 4 ears, but in each case the cholesteatoma was removed, leaving the endosteum intact, without any resulting sensorineural hearing loss.

DISCUSSION

One goal of otologic surgeons is to develop a single technique for cholesteatoma surgery that is amenable to all or most patients.⁹ Certainly, at present, this goal has not been achieved. Most experienced otologic surgeons in the United States use a combination of CWU and CWD techniques, tailoring the surgery to the particular individual or clinical situation. However, in the literature, the selection criteria used to determine a specific operation for an individual patient are extremely variable. Likewise, the results reported by different authors for a given technique vary tremendously. For CWU surgery, Sheehy and Robinson¹⁰ initially reported recurrence rates of 5%, and Glasscock¹¹ reported a 14% recurrence rate. At the other extreme, a review by Cody et al¹² of the Mayo experience showed a 50% recurrence rate, and Mazzoni et al¹³ reported a 33% recurrence rate with the CWD procedure. Nyrop and Bonding's¹⁴ 10-year follow-up of CWU cases in Copenhagen showed that 70% required a later CWD operation. This wide variance in results clearly illustrates the controversy regarding the management of the posterior canal wall and the uncertainty involved with selection criteria for the surgical treatment of cholesteatoma.

Management of the posterior canal wall is a double-edged sword. Preserving the canal wall in the CWU procedure allows, for the most part, better hearing, less postoperative care, and freedom from the lifestyle changes associated with a mastoid cavity.¹⁵ Hearing aid fitting is likewise made simpler. However, preserving the canal wall greatly limits surgical exposure of the epitympanum and posterior mesotympanum, and thus may prevent localization and removal of the entire cholesteatoma, leading to high residual rates. Primary acquired cholesteatomas typically begin in the epitympanum and extend into the antrum, so exposure of this complicated area is essential for complete removal.

Because most cholesteatoma recurrences have been shown to occur in the epitympanum and mesotympanum,¹⁶ exposure of these areas is critical for suc-

cessful cholesteatoma extirpation. In fact, the aspect of CWD surgery that leads to lower recurrence rates is not so much that the mastoid is exteriorized, but that the epitympanum and the oval window area are widely exposed in the process of superior canal wall removal, affording more complete cholesteatoma dissection from these critical areas. Thus, a compromise between the two techniques would be removal of a portion of the canal wall for exposure and extirpation of the cholesteatoma, followed by reestablishment of the canal wall during the reconstruction phase of the surgery — a technique used for retrograde mastoidectomy.

Because of the limitations of traditional CWD and CWU techniques for cholesteatoma removal, the concept of partial canal wall removal for cholesteatoma extirpation coupled with primary reconstruction is being reconsidered. Wullstein¹⁷ recognized the advantage of this concept when she described osteoplastic flap surgery in 1974. A traditional CWU surgery was performed, followed by removal of the canal wall for exposure of the epitympanum, with subsequent reinsertion of the bony segment after cholesteatoma extirpation. Although it certainly offers improved exposure, this technique is somewhat tedious and can be complicated by mobilization and osteonecrosis of the free segment of bone.¹⁸ Others have modified this technique by rigidly fixing the canal remnant with microplates and, frequently, using a vascularized pedicled flap for coverage.¹⁹ Good preliminary results have been reported with these modifications.

I favor removal of the canal wall and reconstruction with cartilage according to the technique described herein. Less drilling is required, and no specialized instrumentation is needed. Autologous cartilage appears to be the ideal material for canal wall reconstruction. Since Szpunar²⁰ first reported on its use, several authors have described techniques for cartilage reconstruction of the scutum and canal wall.^{21,22} The stability of autologous cartilage in the middle ear and mastoid is well established, both clinically and experimentally, and it is readily available at the surgical site. Although many authors describe using tragal cartilage in reconstructive surgery of the middle ear and mastoid, conchal cartilage, particularly that harvested from the cyma area, is more appropriate for canal wall reconstruction.²³ Cyma cartilage tends to be thicker, and the slightly concave shape of its long axis nicely approximates the canal wall. This cartilage is also stiffer, so it can "snap" into the bony grooves, facilitating a nice, tight fit. It can be harvested relatively easily and in sufficient quantity from the postauricular incision. For these reasons, cyma cartilage was used exclusively for canal wall recon-

struction with the retrograde mastoidectomy that I describe.

Other advantages I have found with this approach include decreased surgery times (1 to 1.5 hours), with early exposure of the oval window and facial nerve at the tympanic segment. Likewise, the hearing results compare favorably to those obtained with second-stage reconstruction, with minimal use of Gelfoam.^{1,11,24} Primary reconstruction is an integral component of this technique, as the prosthesis acts to support the cartilage reconstruction of the posterior tympanic membrane and maintain the middle ear space. As a result, the need for Gelfoam to support the tympanic membrane reconstruction, a technique frequently relied upon in staged CWU surgery, is alleviated. Gelfoam has been shown to promote fibrosis when the middle ear mucosa is violated,²⁵ so any technique that reduces the need for Gelfoam as a supporting matrix would be advantageous.

A final consideration is that recent evidence suggests that preserving the mucosa in the antrum and mastoid leads to recovery of aeration and ciliary function in the mastoid during the postoperative period. This is believed by some to be important in the prevention of recurrent cholesteatoma after surgery.²⁶ In contrast to traditional techniques, the retrograde mastoidectomy approach preserves the mucosa in the mastoid and epitympanum, facilitating the functional and anatomic recovery of this system. Advocates of CWU surgery frequently relate that it is necessary to remove all of the "diseased" mucosa from the mastoid — similar to the philosophy that was held concerning paranasal sinus surgery before the introduction of functional sinus surgery. Whereas traditional techniques endeavored to remove all of the mucosa, it was shown that simple aeration of the sinus by opening its natural ostia allowed this "diseased" mucosa to revert to normal. Although the exact function and aeration of the mastoid is currently poorly understood, a similar situation probably exists in the middle ear cleft. Certainly, further research is needed in this area, as clinical experience is beginning to indicate that mastoidectomy in chronic otitis media may not be needed.²⁷

When reporting results for cholesteatoma surgery, it is essential to discuss both recurrence and residual

rates. Residual disease is that which is left behind after the initial surgery and is determined by the method of cholesteatoma exposure and removal. Seventy-five percent of all residual disease manifests by 2 years after operation,²⁸ so the average 45-month follow-up period in this study gives a good indication of what could be anticipated over the long term. Recurrent cholesteatoma, on the other hand, is caused by retractions from the reconstructed tympanic membrane and is dictated not only by the method of reconstruction, but also by other factors, such as eustachian tube function. In my experience, it appears that meticulous reconstruction of the posterior portion of the eardrum with cartilage in close approximation with the canal wall reconstruction offers a significantly better barrier to recurrent retractions in the attic area, in comparison with traditional CWU techniques. However, the surgeon and patient must work diligently to correct the underlying cause of the cholesteatoma and be prepared to intubate the middle ear should severe eustachian tube dysfunction persist in the postoperative period. One must keep in mind that "second-look" surgeries 1 year after the primary surgery affect only the rate of residual disease, and these 2-stage surgeries are still associated with a 10% to 12% recurrence rate, with follow-up, due to retractions in the reconstructed eardrum secondary to continuous eustachian tube dysfunction.^{5,29} These recurrence rates following 2-stage surgery appear to be similar to those reported for the single-stage approach.

With the favorable hearing results and low recurrence rate seen in my series of patients thus far, the efficacy of this approach as a single-stage technique for the treatment of cholesteatoma is becoming apparent. It has proven to be a relatively safe, efficient surgery that can be reproducibly taught to residents and other surgeons. To date, this technique has been performed at our institution as a primary treatment method for over 200 consecutive patients with cholesteatoma, regardless of cholesteatoma size or extent. I have already seen a dramatic decrease in the number of short-term recurrences, in comparison with previous experience with other techniques at our institution.³⁰ Although my short-term results are encouraging, I am currently pursuing a long-term study in this larger series of patients to further examine the efficacy of this technique.

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INFERIOR TURBINECTOMY VERSUS SUBMUCOSAL DIATHERMY FOR INFERIOR TURBINATE HYPERTROPHY

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In order to compare and evaluate bilateral inferior turbinectomy (BIT) and submucosal diathermy (SMD), we retrospectively examined these two well-known techniques for treatment of nasal obstruction due to bilateral congestion of the inferior turbinates. One hundred patients with bilateral nasal obstruction were divided into 4 groups according to their nasal airflow patency. Forty-nine patients underwent BIT, and 51 patients underwent SMD. All 100 patients were followed for 2 months after surgery. Patients with difficult postoperative courses were followed up to 1 year after surgery, in order to decide on the necessity of operative revision. Postoperative improvement in nasal breathing after BIT was reported for 96% of patients 2 weeks after surgery, and for 88% 2 months after surgery. Only 1 BIT patient had to undergo revision operation. Diathermy showed good results in 78% of cases 2 weeks after surgery. The efficacy of the procedure was reduced to 76% 2 months after surgery. Twenty percent of SMD patients were advised to undergo operative revision. Postoperative bleeding occurred in 20% of BIT patients and in only 4% of SMD patients. We found that the extent of postoperative improvement does not depend on preoperative conditions; therefore, it is impossible to predict the extent of postoperative improvement on the basis of the results of preoperative assessment. Both procedures can be performed under local anesthesia, are relatively safe and effective, and do not need expensive instrumentation that may not be available in many medical centers.

KEY WORDS — inferior turbinectomy, submucosal diathermy.

INTRODUCTION

Nasal obstruction is common in the adult population and may affect the patient's health by causing prolonged respiratory infections, secondary sinus involvement, diminution of the sense of smell, and sleep disorders.¹⁻³ The cause of chronic nasal obstruction due to hypertrophic inferior turbinates is usually perennial allergic rhinitis and/or vasomotor rhinitis. The turbinate enlargement in these patients is usually bilateral and is caused by a thickening of the mucosa without hypertrophy of the underlying structures.⁴

Medical treatment, including antihistamines, topical and systemic steroids, desensitization, and allergen avoidance, is used; but if these measures fail, surgery is advised.^{1,5} A long list of surgical procedures has been suggested to deal with hypertrophy of the inferior turbinates,⁵ including submucosal injection of sclerosants or corticosteroids,⁶ cryoturbinectomy,^{7,8} resection of the entire turbinate,^{9,10} submucosal resection of the inferior turbinate,⁶ and laser turbinectomy.^{1,11,12} Resection of obstructive inferior turbinates was first reported in 1895,¹³ and 5 years later, Holmes¹⁴ reported his experience with

turbinectomy in 500 patients. Unfortunately, these procedures are traumatic and are often complicated by postoperative bleeding, infections, dryness, crusting, and adhesions,¹⁵ and a widespread controversy over the safety of resection of the inferior turbinates has continued to this day.

Submucosal diathermy (SMD) of the inferior turbinates was popularized in 1989,¹⁶ although it was reported in 1907.¹⁷ It is believed that the coagulative current produces tissue necrosis and that the ensuing fibrosis causes shrinkage of the soft tissues of the turbinates.^{16,18} The SMD technique is usually associated with rapid healing leading to early restoration of normal maxillary function, and many surgeons use SMD as the treatment of choice because of its relative lack of complications.¹⁹

In Haifa, there are 2 main linked hospitals, the Rambam and Bnai Zion Medical Centers. In the Rambam Medical Center, the surgical treatment routinely used for hypertrophy of the inferior turbinates is inferior turbinectomy by the technique described by Ophir et al,² and in Bnai Zion Medical Center, SMD is routinely used by inserting an Abbey diathermy needle into the anterior end of the inferior turbinate and ad-

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TABLE 1. PREOPERATIVE NASAL AIRFLOW MEASURED BY GERTNER-PODOSHIN PLATE

Group	Nasal Breathing (cm)	BIT		SMD	
		No.	%	No.	%
1	0-1	11	22	6	12
2	2-3	29	59	37	73
3	4-5	8	16	7	14
4	6-9	1	2	1	2

See Gertner et al²⁰ for method.

BIT — bilateral inferior turbinectomy, SMD — submucosal diathermy.

vancing it until the posterior end is judged to have been reached.¹⁶ Both procedures are done under local anesthesia using topical 10% cocaine hydrochloride and 1.8 mL of 2% lidocaine hydrochloride with epinephrine (1:100,000). We thought it to be of interest to compare the results and the efficacy of these widely practiced procedures.

The comparison included clinical data, airflow measurement by a Gertner-Podoshin nasal plate,²⁰ olfactory tests, and postoperative complications. The Gertner-Podoshin plate is a simple method of measuring the breathing function of the nose.²⁰ The instrument itself is a polished metal chrome-coated plate, 10 × 12 cm, marked with lines 1 cm apart. The method is based on measuring the area of vapor condensing on the plate. The difference in temperature between the breath from the nose and the air on the plate allows the vapor in the air to be condensed on the colder metal plate, which must be held under the nostrils in a horizontal position in such a way that the vertical axis of the plate is 90° toward the upper lip and straight under the columella nasi. The patient is instructed to breathe through the nose slowly without force and with a closed mouth. This method of measuring the nasal airway was reported in 1984²⁰ and is widely used.

Because doubts have been raised in the literature about the practical relevance of rhinomanometry,^{5,21} in our study rhinomanometry was not performed.

PATIENTS AND METHODS

The charts of 450 patients suffering from nasal obstruction were reviewed. Only 100 patients (49 from the Rambam Medical Center and 51 from the Bnai Zion Medical Center) met the criteria of the study. Patients who had undergone a prior nasal operation or who suffered from chronic sinusitis, nasal polyps, or septal deviation were excluded from the study.

Submucosal diathermy was performed under topical anesthesia using 10% cocaine hydrochloride solution and 1.8 mL of 2% lidocaine hydrochloride with epinephrine. A diathermy needle was inserted into

the anterior end of the inferior turbinate and advanced submucosally until the posterior end of the inferior turbinate was judged to have been reached. The needle was withdrawn over a period of 10 seconds with the current applied. This procedure was performed twice on each inferior turbinate. A Vaseline gauze pack was inserted, when necessary, to control hemorrhage and was removed the following morning. A follow-up visit was scheduled for 2 weeks after surgery.

Bilateral inferior turbinectomy (BIT) was carried out under local anesthesia using cotton pledgets moistened with 10% cocaine hydrochloride solution. In addition, in order to complete the anesthesia and reduce the bleeding, the inferior turbinate was infiltrated with 1.8 mL of a mixture of 2% lidocaine hydrochloride and epinephrine (1:100,000) by means of a 23- or 25-gauge spinal needle. A No. 15 blade was used to incise the anterior insertion of the turbinate, down to the conchal bone. The turbinectomy was further performed with angled scissors that were advanced posteriorly as far as possible, so that the resection included the mucosa and the underlying bone. If, after removal of the turbinate, a hypertrophic posterior turbinal tip remained, a snare or a forceps was used to complete the resection. After excision, the nasal airways were packed with Vaseline gauze or Merocel nasal packs, which were removed 48 to 72 hours after the operation. A follow-up visit was scheduled for 2 weeks after surgery.

Both BIT and the SMD were performed in the operating room under the supervision of a senior anesthesiologist.

All the patients had 3 measurements of nasal flow by means of the Gertner-Podoshin plate²⁰: one before the operation, a second 2 weeks after the operation, and the third 2 months after the operation, which was also the final assessment if there were no complaints from the patient. If the patient complained about breathing difficulties, he or she was followed for up to 1 year and underwent another operation if necessary.

The patients were divided into 4 groups according to nasal airflow as measured by the Gertner-Podoshin plate (Table 1²⁰): group 1, with severe nasal obstruction; group 2, with moderate nasal obstruction; group 3, with mild nasal obstruction; and group 4, with very mild nasal obstruction. Three patients who underwent SMD and 1 of the BIT group had a history of nasal trauma in childhood. Three patients who underwent SMD and 1 patient from the turbinectomy group had previous diagnoses of sleep apnea syndrome (SAS). All the patients were questioned about nasal obstruction, chronic discharge from the nose, snoring, headaches, and hyposmia or anosmia.

TABLE 2. SUBJECTIVE ESTIMATE OF NASAL BREATHING BEFORE SURGERY

State of Nasal Breathing	BIT		SMD	
	No.	%	No.	%
No difficulty	1	2	1	2
Mild difficulty on physical effort	1	2	4	8
Difficulty on effort	26	53	15	29
Difficulty at rest	21	43	31	61

The nasal obstruction was divided as follows (Table 2): 0, no breathing difficulty; 1, mild breathing difficulty on physical effort; 2, breathing difficulty on physical effort; and 3, breathing difficulty at rest.

All patients underwent thorough anterior and posterior rhinoscopy and a measurement of the airflow by the Gertner-Podoshin nasal plate.²⁰ Forty-nine patients underwent subtotal inferior turbinectomy (Rambam Medical Center), and 51 underwent SMD of the inferior turbinates (Bnai Zion Medical Center). The operations were performed under local anesthesia in adults and under general anesthesia in children under the age of 16 years.

The first postoperative assessment was made in both hospitals 2 weeks after the operation, and the final one 2 months after the operation. The assessment included a questionnaire about breathing through the nose, anterior and posterior rhinoscopy, and nasal airflow measurement with the Gertner-Podoshin plate. Patients who had no complaints and had normal airflow were not followed up. Patients who continued to complain about nasal obstruction or had an abnormal airflow measurement with the Gertner-Podoshin plate were followed up in our outpatient clinic, were treated conservatively, and if the treatment did not help, underwent reoperation.

The results were analyzed statistically by the Student's *t*-test. A *p* value of <.05 was considered statistically significant.

RESULTS

Nasal airflow as measured by the Gertner-Podoshin nasal plate is shown in Table 1, and subjective complaints of preoperative nasal obstruction are summarized in Table 2.

Three patients who underwent SMD (6%) and 1

TABLE 3. PREOPERATIVE PATIENT COMPLAINTS

Complaint	BIT		SMD	
	No.	%	No.	%
Chronic nasal discharge	34	69	23	45
Headaches	3	6	3	6
Hyposmia	21	43	20	39
Sleep apnea syndrome	1	2	3	6

TABLE 4. SUBJECTIVE ESTIMATE OF NASAL BREATHING TWO WEEKS AFTER SURGERY

State of Nasal Breathing	BIT		SMD	
	No.	%	No.	%
Free breathing	23	47	17	33
Significant improvement	19	39	17	33
Mild improvement	5	10	6	12
No improvement	2	4	10	20
Worsening	0	0	1	2

patient who underwent BIT had a history of nasal trauma in childhood. Three patients in each group (6%) complained about chronic headaches. Computed tomography (CT) of the brain and nasal sinus was performed in all of these patients, and the CT scans were without pathological findings.

Three patients (6%) from Bnai Zion Medical Center and 1 patient (2%) from Rambam Medical Center received diagnoses of SAS at the Sleep Laboratory of the Technion-Israel Institute of Technology. These patients underwent operation as a first-stage treatment for SAS. Ten patients from the SMD group and 21 patients from the BIT group complained of hyposmia (Table 3). The patients' complaints are summarized in Table 3.

The first postoperative assessment was made 2 weeks after the surgery. At this stage, 40 patients (78%) who underwent SMD and 47 patients (96%) who underwent BIT reported an improvement in nasal breathing (Table 4). Two BIT patients (4%) and 10 SMD patients (20%) reported no improvement, and 1 SMD patient (2%) reported worsening in nasal breathing.

The results of the airflow measurements made with the Gertner-Podoshin plate 2 weeks after surgery are summarized in Table 5.²⁰ The difference between the preoperative and postoperative states in both types of treatment was statistically significant (*p* < .005).

The next assessment was made 2 months after surgery. At this stage, 4 BIT patients (8%) and 3 SMD patients (6%) reported a further improvement in nasal breathing, whereas 5 BIT patients (10%) and 5

TABLE 5. OBJECTIVE ASSESSMENT OF NASAL AIRFLOW BY GERTNER-PODOSHIN PLATE TWO WEEKS AFTER SURGERY

Nasal Breathing (cm)	BIT		SMD	
	No.	%	No.	%
0-1	1	2	0	0
2-3	1	2	2	4
4-5	2	4	8	16
6-7	12	24	16	31
8-9	33	67	25	49

See Gertner et al²⁰ for method.

TABLE 6. SUBJECTIVE ESTIMATE OF NASAL BREATHING TWO MONTHS AFTER SURGERY

State of Nasal Breathing	BIT		SMD	
	No.	%	No.	%
Free breathing	39	80	36	70
Improved compared to prior examination	4	8	3	6
No improvement	1	2	7	14
Worse compared to prior examination	5	10	5	10

SMD patients (10%) complained of worsening of nasal obstruction and 1 BIT patient (2%) and 7 SMD patients (14%) reported no change (Table 6). A total of 43 BIT patients (88%) and 39 SMD patients (76%) were satisfied with the results of surgery 2 months after surgery.

The results of the airflow measurements made with the Gertner-Podoshin plate are summarized in Table 7.²⁰ Statistical analysis showed a significant difference between the two operations ($p < .01$).

At the 2-month assessment, no patient that had suffered from chronic nasal discharge reported healing, although 58% of BIT patients and 57% of SMD patients reported some improvement (Table 8). Out of 21 BIT patients and 20 SMD patients who had complained of hyposmia before surgery, 9 BIT patients (43%) and 8 SMD patients (40%) reported improvement in their sense of smell ($p > .05$). Three patients from each group had complained of headaches before surgery; after the operation, 2 patients from each group reported that the headaches had disappeared.

Eight patients (16%) from the BIT group and 15 patients (30%) from the SMD group were dissatisfied with the results of the operation, and all were treated conservatively. Of those patients who were not helped by conservative treatment, 1 BIT patient and 10 SMD patients underwent reoperation. We have no definite explanation of why there was such a discrepancy between the two methods. A failure of the SMD technique, which was only recently introduced, may explain this difference between the two groups.

The postoperative complications were primary (in

TABLE 7. POSTOPERATIVE AIRFLOW ASSESSMENT BY GERTNER-PODOSHIN PLATE TWO MONTHS AFTER SURGERY

Nasal Breathing (cm)	BIT		SMD	
	No.	%	No.	%
0-1	1	2	0	0
2-3	1	2	5	10
4-5	4	8	7	14
6-7	13	27	16	31
8-9	30	61	23	45

See Gertner et al²⁰ for method.

TABLE 8. SUBJECTIVE ESTIMATE OF NASAL DISCHARGE TWO MONTHS AFTER SURGERY

State of Discharge	BIT		SMD	
	No.	%	No.	%
Present preoperatively	34	69	23	45
No discharge	0	0	0	0
Significant improvement	11	32	8	35
Mild improvement	9	26	5	22
No improvement	14	41	10	43

the first 24 hours after surgery) and secondary bleeding; infection; and nasal crusting. Ten BIT patients (20%) and 2 SMD patients (4%) had postoperative bleeding; 2 patients (4%) from each group suffered from postoperative infection; and 5 BIT patients (10%) and 3 SMD patients (6%) had nasal crusting (Table 9).

DISCUSSION

Nasal obstruction is probably the most common chronic presenting symptom encountered by otolaryngologists.¹² Most patients with nasal obstruction have turbinate hypertrophy due to vasomotor, allergic, or perennial rhinitis.^{1,2,12} Most cases are mild and respond to antihistamine-decongestant preparations or allergy desensitization, but in some cases surgery is required.¹² The surgical treatment is controversial, and many surgical methods of treatment have been proposed.^{2-4,6-8,10,16}

Nasal Obstruction. In the present work, we compared 2 widespread methods of surgical treatment, BIT and SMD, in 100 patients. Two weeks after surgery, the success of the operation for nasal obstruction was 96% for the BIT patients and 78% for the SMD patients ($p < .005$). Similar success rates were reported by Ophir et al² and Englander.¹ In addition, 26% of SMD patients reported improvement in nasal obstruction 2 months after surgery, whereas 12% of BIT patients and 24% of SMD patients had no significant improvement in the nasal airway and were followed longer. In the first year after the operation, 4% of BIT patients and 6% of SMD patients returned to the outpatient clinic complaining of worsening of nasal breathing. One BIT patient and 10 SMD patients underwent reoperation ($p < .005$).

From these results, we can conclude that BIT (96% success rate) is more effective in relieving nasal ob-

TABLE 9. POSTOPERATIVE COMPLICATIONS

Complication	BIT		SMD	
	No.	%	No.	%
Hemorrhage	10	20	2	4
Infection	2	4	2	4
Crusting	5	10	3	6

struction than SMD (78% success rate). The long-term effectiveness of inferior turbinectomy was assessed in 186 patients by Ophir et al,² who reported relief of nasal obstruction in 82% of patients and showed a clean and wide airway in 88% of patients. Rakover and Rosen,⁴ who compared the effectiveness of partial inferior turbinectomy with that of cryosurgery in 52 patients, reported 77% relief of nasal obstruction in the partial turbinectomy group versus a 62% success rate after 1 year in the cryosurgery group. The SMD method was compared to cryosurgery in 26 patients (13 in each group), and the two methods were found to be equally effective in relieving nasal obstruction.¹⁸

Before surgery, we could not predict the outcome of the operation. All the patients who underwent BIT or SMD had engorged inferior turbinates and underwent the same procedure, but in some patients the outcome of the operation was different and the relief of nasal obstruction was not achieved, and 2% of the BIT patients and 20% of the SMD patients had to undergo the same procedure again. There was a significant difference between outcomes in terms of nasal obstruction for the two methods; the BIT patients had greater improvement in their nasal breathing after surgery. A partial failure of the SMD technique could result if the diathermy needle did not always reach the posterior end of the inferior turbinate, and this may explain the difference in the postoperative outcomes.

Nasal Discharge. Fifty-eight percent of patients in the BIT group and 57% of patients in the SMD group who suffered from chronic nasal discharge reported some improvement after surgery. There are similar reports in the literature,^{22,23} but there is also a consensus that turbinectomy by SMD is not the treatment of choice for relieving nasal discharge.^{10,24}

Olfactory Acuity. Forty-three percent of the BIT group and 40% of the SMD group reported an improvement in olfactory acuity. Improvement of olfactory acuity has been reported in the literature after turbinectomy.^{5,25} We did not find any reports about changes in olfactory acuity after SMD.

Headaches. Headaches may, rarely, occur in chronic rhinitis.^{1,3,22,23} In our study, 6% of the BIT group and 6% of the SMD group reported an improvement

of headaches. As the number of patients was small, no significant conclusions could be drawn.

Postoperative Complications. Postoperative bleeding occurred in 20% of the BIT patients and in only 9% of the SMD patients. In 10% of the BIT patients, the bleeding was massive and needed intranasal packing. In no patient from the SMD group was the bleeding massive. Bleeding following BIT is reported in the literature, ranging from 4% to 28%,²⁶ but bleeding following SMD is rare.^{16,18,19} Another complication of both procedures is nasal crusting.^{4,5,10,19} In our study, 10% of the BIT group and 6% of the SMD group had nasal crusting. This problem was promptly resolved within a few days by irrigation with normal saline solution. The percentage of patients with nasal crusting has been reported in the literature to be much higher, but our study was performed in Haifa and the northern part of Israel, which has no cold winters and no arid summers. The high humidity of our region could explain the low rate of crusting after BIT. No case of atrophic rhinitis, adhesions, or inferior turbinate necrosis occurred in our study.

SUMMARY

In the present study, two widely practiced surgical procedures for reduction of the size of the inferior turbinates were evaluated and compared in 100 patients. The effectiveness of BIT in relieving nasal obstruction was 96% 2 weeks after surgery and 88% 2 months after surgery. Only 1 patient had to undergo a revisional operation. Submucosal diathermy showed good postoperative results in 78% of cases 2 weeks after surgery, and in 76% 2 months after surgery. Ten patients had to undergo a revisional operation. There were no statistically significant differences in enhanced olfactory acuity, nasal discharge, or improvement of headaches between the two methods. Postoperative bleeding occurred in 20% of the BIT patients and in 4% of the SMD patients. The extent of postoperative improvement could not be predicted on preoperative assessment. Both procedures can be performed under local anesthesia and do not require expensive instrumentation that may not be available in many medical centers. Both procedures are relatively safe and effective in relieving nasal obstruction caused by chronic obstructive inferior turbinates, although SMD is more effective in the short term and could be disappointing on a long-term basis.

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PROLIFERATION MARKERS, PROLIFERATING CELL NUCLEAR ANTIGEN, Ki67, 5-BROMO-2'-DEOXYURIDINE, AND CYCLIN D1 IN MOUSE OLFACTORY EPITHELIUM

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We immunohistochemically identified proliferating cells in the olfactory epithelium of mice, using an anti-proliferating cell nuclear antigen (PCNA) antibody, an anti-Ki67 antibody, an anti-5-bromo-2'-deoxyuridine (BrdU) antibody, and an anti-cyclin D1 antibody. Positive cells stained by the 4 antibodies were identified mainly in the basal layer. The mean numbers of positive cells stained by the 4 antibodies in 500 olfactory epithelium cells from each animal were as follows: PCNA-positive cells 42, Ki67-positive cells 23, BrdU-positive cells 13.7, and cyclin D1-positive cells 9.2. PCNA may be detected in both proliferating and resting cells. Ki67 is an intranuclear antigen expressed in proliferating, but not resting, cells. Anti-BrdU antibodies might stain proliferating cells only following the S-phase, but not the G1-phase. Cyclin D1 is a protein that works during the G1-phase of the cell cycle. When we stain proliferating cells using proliferating cell markers, it is important to consider the cell cycle phases during which each marker stains.

KEY WORDS — BrdU, cyclin D1, Ki67, olfactory epithelium, PCNA.

INTRODUCTION

The olfactory epithelium is unique in its ability to give rise to new sensory neurons throughout life, and neurogenesis is greatly enhanced after injury to the epithelium, allowing for rapid reconstitution of the damaged epithelium. Therefore, proliferating cells exist in the olfactory epithelium, even in adult animals.¹ Anti-5-bromo-2'-deoxyuridine (BrdU) antibodies have been used to identify proliferating cells immunohistochemically,^{2,3} and previously, we used an anti-proliferating cell nuclear antigen (PCNA) antibody to identify proliferating cells immunohistochemically. By these methods, some proliferating cells were identified in the basal layer of the olfactory epithelium of adult mice. A few proliferating cells were also noted in the surface and intermediate layers.

PCNA is a nuclear polypeptide whose synthesis correlates with G1- and S-phases in proliferating cells.⁴ Ki67 is an intranuclear antigen expressed in proliferating (G1-, S-, G2-, and M-phase) cells, but not resting (G0-phase) cells.⁵ BrdU can be introduced to proliferating cells during the S-phase.⁵ Cyclin D1 is a protein that works during the G1-phase of the cell cycle.⁶

Anti-Ki67 antibodies and anti-cyclin D1 antibodies have been used to clarify proliferating cell expression immunohistochemically.^{7,8} Accordingly, we identified proliferating cells, using an immunohistochemical method with 4 antibodies — an anti-PCNA

antibody, an anti-Ki67 antibody, an anti-BrdU antibody, and an anti-cyclin D1 antibody — and compared positive cells stained by the 4 antibodies in the olfactory epithelium of mice.

MATERIALS AND METHODS

We examined 6 adult (postnatal week 6) mice. We injected BrdU in each mouse at 1 to 1.5 hours before fixation. Each mouse was then decapitated to provide whole-head specimens, and the specimens were decalcified in 10% ethylenediaminetetraacetic acid. The fixed specimens were embedded in paraffin and cut into 4- μ m-thick sections. After microwave treatment, the sections were incubated for 24 hours at 4°C with anti-PCNA monoclonal IgG (Oncogene Research Products, Cambridge, Mass), anti-Ki67 polyclonal IgG (Novocastra Laboratories Ltd, Newcastle, England), anti-BrdU monoclonal IgG (Novocastra Laboratories Ltd), and anti-cyclin D1 monoclonal IgG (MBL, Nagoya, Japan) as the primary antibodies. Immunohistochemical staining was performed with an LSAB kit (Dako Japan, Kyoto, Japan). The immunoreactive antibody-antigen complexes were visualized with 3,3'-diaminobenzidine tetrahydrochloride (DAB). After staining, we compared PCNA-, Ki67-, BrdU-, and cyclin D1-positive cells in the sections.

RESULTS

In the olfactory epithelium of the 6 mice, PCNA-, Ki67-, BrdU-, and cyclin D1-positive cells were identified abundantly in the basal layers. Ki67- and BrdU-

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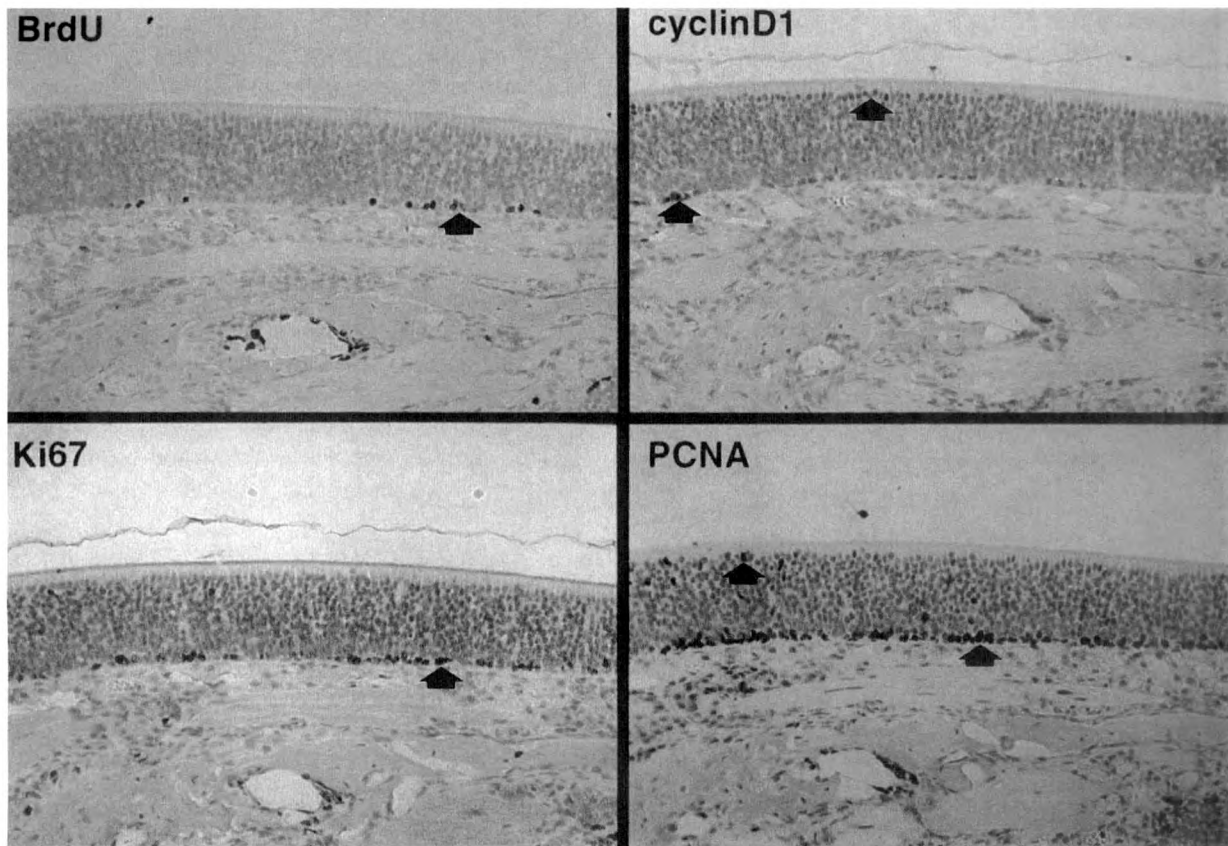


Fig 1. Olfactory epithelium of postnatal week 6 mouse stained by anti-BrdU monoclonal IgG, anti-cyclin D1 monoclonal IgG, anti-Ki67 polyclonal IgG, and anti-PCNA monoclonal IgG (diaminobenzidine and hematoxylin, original $\times 100$). Arrows — proliferating cells.

positive cells were scarce in the surface and intermediate layers. A few PCNA- and cyclin D1-positive cells were identified in the surface layers (Fig 1). The mean number of PCNA-positive cells observed in 500 olfactory epithelium cells from each animal was 42, that of Ki67-positive cells was 23, that of BrdU-positive cells was 13.7, and that of cyclin D1-positive cells was 9.2 (Fig 2).

DISCUSSION

PCNA is a nuclear polypeptide that functions as a

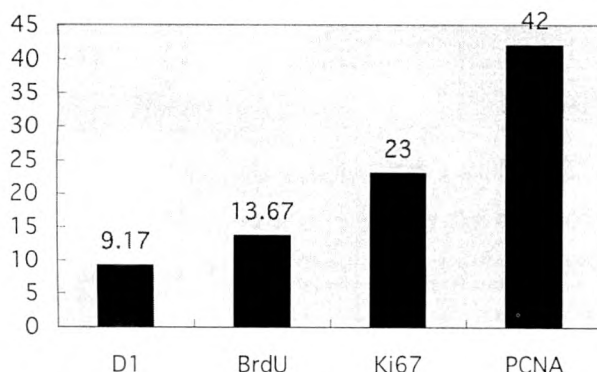


Fig 2. Mean cyclin D1-, BrdU-, Ki67-, and PCNA-positive cell numbers in 500 olfactory epithelium cells from each animal.

co-factor for DNA polymerase delta during the S-phase⁴ and DNA synthesis associated with DNA damage repair mechanisms. PCNA molecules have a half-life in excess of 20 hours. Therefore, PCNA may be detected in resting (G0-phase) cells.

Ki67 is an intranuclear antigen that is expressed in all phases of a proliferating cell cycle (G1-, S-, G2-, and M-phases), but is absent from resting (G0-phase) cells.⁵ An anti-Ki67 antibody was first obtained in studies aimed at the production of antibodies to nuclear antigens specific to Hodgkin and Sternberg-Reed cells. Later, however, it was found to react with a nuclear antigen restricted to cells that are known to proliferate.⁹

BrdU is an analog of thymidine. BrdU can be introduced into proliferating cells, which incorporate BrdU into DNA during the S-phase, prior to cell division.⁵

The D-type cyclins are a family of proteins that function primarily by regulating the activity of cyclin-dependent protein kinases in the G1-phase of the cell cycle. The maximum expression of cyclin D1 occurs at a critical point in the middle-to-late G1-phase of the cell cycle.⁶

In our study, PCNA-positive cells were the most numerous of the 4 kinds of positive cells. This result may be due to nonspecific persistence of PCNA in all stages of the cell cycle.

We believe that the detection of proliferating cells by anti-BrdU antibody is appropriate, because it stains BrdU that is injected. Other antibodies stain polypeptides that already exist in the cells. However, using an anti-BrdU antibody needs consideration for several reasons. First, an anti-BrdU antibody might stain proliferating cells after the S-phase, but not the G1-phase. Second, it takes at least about 1 to 1.5 hours from injecting BrdU into the mouse until fixation, so it is possible that the proliferating cells change their position in the olfactory epithelium.

The D1-positive cells were the least numerous of the 4 kinds of positive cells. This result is due to the fact that anti-cyclin D1 antibody reacted with proliferating cells in the shortest time. In some sections, some supporting cells reacted with the anti-cyclin D1 antibody. However, they did not react with anti-Ki67 antibody. If they were true proliferating cells, they would have reacted with anti-Ki67 antibody. Accordingly, we think they were overstained.

Anti-Ki67 antibodies are used widely as antibodies

that show proliferating cells in all phases of the cell cycle (G1-, S-, G2-, and M-phases), but are absent from resting (G0-phase) cells. It is more appropriate to clarify the expression of all phases of proliferating cells in the olfactory epithelium by using the anti-Ki67 antibody rather than the anti-PCNA antibody.

CONCLUSIONS

1. We immunohistochemically identified proliferating cells in the olfactory epithelium of mice, using an anti-PCNA antibody, an anti-Ki67 antibody, an anti-BrdU antibody, and an anti-cyclin D1 antibody. Positive cells stained by the 4 antibodies were identified mainly in the basal layer.

2. Anti-BrdU antibodies might stain proliferating cells following the S-phase, but not the G1-phase.

3. Anti-Ki67 antibodies, rather than anti-PCNA antibodies, are more appropriate for clarifying the expression of all phases of proliferating cells in the olfactory epithelium.

4. When we stain proliferating cells using proliferating cell markers, it is important to consider the cell cycle phases during which each marker stains.

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ROLE OF NEUTROPHIL ELASTASE IN ENDOTOXIN-INDUCED MUCUS HYPERSECRETION IN RAT NASAL EPITHELIUM

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In the present study, hypertrophic and metaplastic changes of goblet cells were induced in rat nasal epithelium by intranasal instillation of endotoxin or elastase. A significant increase in the amount of intraepithelial mucosubstance was observed after 24 hours during 3 days of instillation. The elastase-induced mucus production was not inhibited in neutrophil-depleted rats, but the endotoxin-induced change was significantly inhibited. Intranasal instillation of the neutrophil elastase inhibitor ONO-5046 partially inhibited the endotoxin-induced mucus production. Epithelial mucus secretion was evaluated by the temporary decrease in the amount of intraepithelial mucosubstance. The endotoxin-induced mucus secretion peaked 3 to 6 hours after intranasal instillation, coinciding with the peak of the intraepithelial neutrophil infiltration. The elastase-induced mucus secretion peaked 1 to 3 hours after intranasal instillation; intraepithelial neutrophil infiltration was not induced by elastase. These results indicate that neutrophil elastase is an important mediator of the intraepithelial mucus synthesis and secretion induced by endotoxin.

KEY WORDS — airway, elastase, endotoxin, interleukin-8, lipopolysaccharide, mucus, neutrophil, nose, rat.

INTRODUCTION

Mucus hypersecretion is a common clinical observation in airway diseases such as rhinitis, sinusitis, tracheobronchitis, and asthma. However, the mechanism of this increased mucus synthesis and secretion is not well understood. Many inflammatory stimuli, such as inhalative irritants,^{1,2} neutrophil products,³⁻⁵ and viral or bacterial infections,⁶ have been used to study the mechanism of mucus hypersecretion in the respiratory epithelium. In the present study, hypertrophic and metaplastic changes of goblet cells were induced in rat nasal epithelium by intranasal instillation of endotoxin; the intraepithelial mucosubstance increased significantly after 24 hours during 3 days of endotoxin instillation. This endotoxin-induced change was significantly inhibited in rats with neutrophil depletion induced by the intraperitoneal injection of anti-rat neutrophil antiserum or cyclophosphamide.⁷ These results indicate that neutrophils are involved in the mucus hypersecretion that occurs during endotoxin instillation.

Neutrophils produce and secrete oxygen metabolites, various enzymes, bioactive lipids, cytokines, lactoferrin, and defensins.⁸ Among these products, neutrophil elastase is believed to play an important role in mucus hypersecretion from epithelial cells and submucosal glands; intratracheal instillation of neutrophil elastase induced mucus production and secretory cell metaplasia in hamsters^{3,4} and rats.⁵ We hy-

pothesized that neutrophil elastase may be an important and direct mediator of endotoxin-induced mucus production.

In the present study, we evaluated 1) whether intranasal instillation of elastase can induce hypertrophic and metaplastic changes of goblet cells in rat nasal epithelium, 2) the effect of neutrophil depletion on elastase-induced intraepithelial mucus production compared with that induced by endotoxin, 3) the effect of neutrophil elastase inhibitor ONO-5046 on endotoxin-induced intraepithelial mucus production, and 4) the time course of intraepithelial mucosubstance and intraepithelial neutrophil infiltration during intranasal instillation of endotoxin or elastase.

MATERIALS AND METHODS

Animals and Tissue Preparations. Male F344 rats (specific pathogen-free, Japan SLC, Inc, Shizuoka, Japan) 8 to 10 weeks of age were used in this study. Porcine pancreatic elastase was used to examine the direct effect of elastase on mucus production; its effect on mucus hypersecretion is similar to that of neutrophil elastase.^{3,9} Rats were anesthetized with ether, and 0.1 mL of saline solution containing 0.1 mg of lipopolysaccharide (LPS, endotoxin) from *Escherichia coli* 0111:B4 (Sigma Chemical Co, St Louis, Mo), 0.5 mg of elastase (type I, from porcine pancreas; Sigma Chemical Co), or 0.5 µg of human recombinant interleukin (IL)-8 (Wako Pure Chemical

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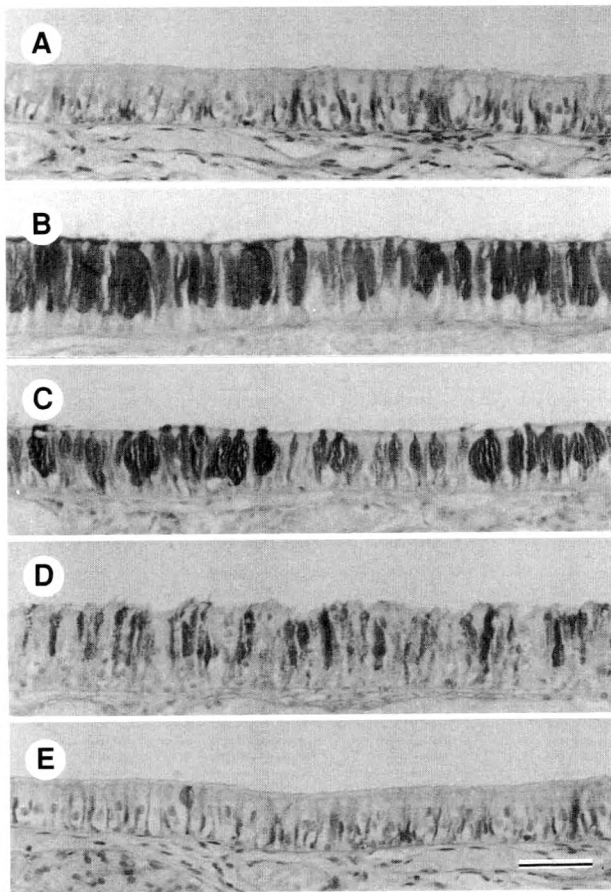


Fig 1. Effects of endotoxin, elastase, and interleukin (IL)-8 instillation on nasal septal epithelium. A) Untreated control. B-D) Hypertrophic and metaplastic changes of goblet cells after B) endotoxin (0.1 mg), C) elastase (0.5 mg), or D) IL-8 (0.5 µg) instillation. IL-8 induced intraepithelial infiltration of many inflammatory cells. E) Saline-treated control. Bar — 30 µm.

Ltd, Osaka, Japan) was instilled into the airways of the nasal cavity for 3 days. The instillation and tissue preparations were carried out as previously described.⁷ The instillate was deposited as a bead of fluid on the external nares and the rats were allowed to aspirate it. Control rats were instilled with saline solution.

Twenty-four hours after the last instillation, 5 rats were painlessly sacrificed with an intraperitoneal overdose of sodium pentobarbital. The head of each rat was removed and fixed in 10% neutral buffered formalin for 24 hours, then decalcified in 5% trichloroacetic acid for 5 days. The nasal cavity was transversely sectioned at the level of the incisive papilla of the hard palate. The tissue block was embedded in paraffin. Five-micron-thick sections were stained with Alcian blue (pH 2.6)-periodic acid-Schiff and hematoxylin (AB-PAS-H).

Morphometry. The percent area of AB-PAS-stained mucosubstance in the epithelial surface was deter-

mined with an image analyzer (SP 500, Olympus, Tokyo, Japan) on 5-µm-thick paraffin sections. The area of the nasal epithelium was outlined, and the area of AB-PAS-stained mucosubstance was determined with the image analyzer. The percent area of stored mucosubstance in the epithelial surface was calculated over 2 mm (1 mm on each side of the nasal septum $\times 2$) of the basal lamina at the center of the septal cartilage. The number of intraepithelial polymorphonuclear cells was also counted over 1 mm (0.5 mm on each side of the nasal septum $\times 2$) of the basal lamina at the center of the septal cartilage with an oil immersion objective lens ($\times 1,000$ magnification).

Neutrophil Depletion. To induce depletion of circulating blood neutrophils, we gave 5 rats intraperitoneal injections of 1 mL of rabbit anti-rat neutrophil antiserum (Inter-Cell Technologies, Hopewell, NJ) for 3 days and gave 5 rats injections of 20 mg of cyclophosphamide (Endoxan, Shionogi Pharmaceutical Co, Osaka) for 5 days before they were sacrificed. As controls, 5 rats were treated with saline solution.

Neutrophil Elastase Inhibitor (ONO-5046). The ONO-5046 (sodium N-[2-[4-(2,2-dimethylpropionyloxy) phenylsulfonylamino] benzoyl] aminoacetate tetrahydrate) was a kind gift from Ono Pharmaceutical Co, Ltd (Osaka).¹⁰ At 1 hour before endotoxin instillation, 6 rats were intranasally instilled with 0.1 mL of saline solution containing 1.5 mg of ONO-5046 for 3 days. As controls, 6 rats were instilled with saline solution.

Statistics. All data are expressed as mean $\pm$ SD. The differences between variables were analyzed by the Mann-Whitney test. Probability values of $p < .05$ were considered statistically significant.

RESULTS

The effects of endotoxin (0.1 mg), elastase (0.5 mg), and IL-8 (0.5 µg) instillation on rat nasal septal epithelium are described in Fig 1. Only a few goblet cells were observed in untreated or saline-instilled control rats. A significant increase in the number of goblet cells was observed 3 days after intranasal instillation of endotoxin or elastase. Inflammatory cell infiltration was observed in the submucosal layer. Intranasal instillation of IL-8 induced intraepithelial neutrophil infiltration in 2 of 5 rats; IL-8-induced mucus production was observed only in these 2 rats, concomitantly with the intraepithelial neutrophil infiltration. Endotoxin or elastase induced significant mucus production in all 5 rats. The quantitative changes in the percent area of intraepithelial mucosubstance of this epithelium are shown in Fig 2. A significant increase in the amount of intraepithelial

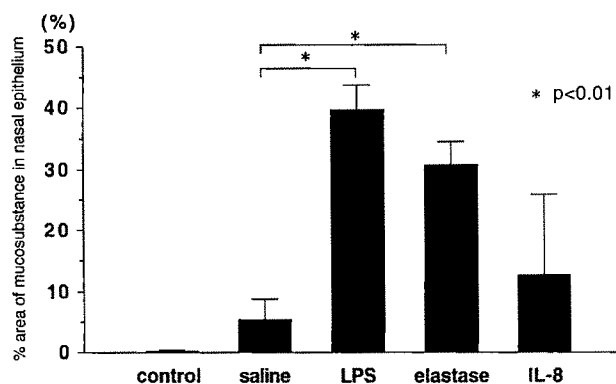


Fig 2. Percent area of mucosubstance in nasal epithelium after 3 days of endotoxin (lipopolysaccharide [LPS]), elastase, or IL-8 instillation. Endotoxin and elastase induced significant increase of epithelial mucosubstance, compared with saline exposure ($n = 5$). IL-8-induced mucus production was observed only in 2 of 5 rats examined; mean percent area of mucosubstance in these 2 rats was 26.1%.

mucosubstance was induced by intranasal instillation of endotoxin or elastase.

The number of circulating white blood cells and the percent area of mucosubstance in neutrophil-depleted rats are shown in Fig 3. Polymorphonuclear cells were almost completely depleted by the intraperitoneal injection of anti-rat neutrophil antiserum or cyclophosphamide. Elastase-induced epithelial mucus production was not inhibited in these neutrophil-depleted rats.

The Table shows the comparison of the mean percent change of stored epithelial mucosubstance in rats with neutrophil depletion induced by elastase (this study) or endotoxin (from Shimizu et al⁷). In the previous study, the effects of neutrophil depletion were studied 3 days after intranasal instillation of 0.5 mg of endotoxin. The methods of endotoxin instillation and neutrophil depletion were the same as those used in this study. Endotoxin-induced epi-

COMPARISON OF MEAN PERCENT CHANGES OF AREA OF MUCOSUBSTANCE IN RAT NASAL EPITHELIUM WITH NEUTROPHIL DEPLETION INDUCED BY ELASTASE OR ENDOTOXIN

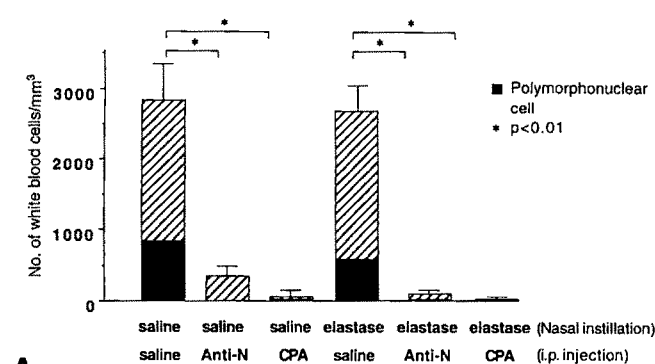
	Method of Neutrophil Depletion	
	Anti-N	CPA
Elastase ($n = 5$)	+2.6%	+5.4%
Endotoxin ($n = 5$)*	-71.8%	-88.5%

Methods of neutrophil depletion are described in Materials and Methods.
Anti-N — rabbit anti-rat neutrophil antiserum; CPA — cyclophosphamide.
*From Shimizu et al.⁷

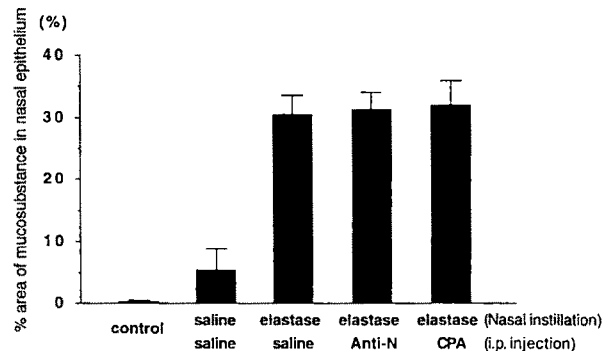
thelial mucus production was significantly inhibited in the neutrophil-depleted rats; however, elastase-induced mucus production was not affected.

The effect of the neutrophil elastase inhibitor ONO-5046 on endotoxin-induced epithelial mucus production is shown in Fig 4. Endotoxin-induced mucus production was partially inhibited by intranasal instillation of ONO-5046 1 hour before endotoxin instillation.

The time course of the amount of intraepithelial mucosubstance and the number of intraepithelial neutrophils found after intranasal instillation of elastase or endotoxin are described in Fig 5. Intraepithelial mucus production was induced 3 days after endotoxin instillation. Then, elastase or endotoxin was intranasally instilled again. Animals were killed 0, 1, 3, 6, 12, and 24 hours after the last instillation. The amount of epithelial mucosubstance decreased temporarily after elastase or endotoxin instillation and recovered 24 hours after the instillation. This transient decrease of intraepithelial mucosubstance was lowest 1 to 3 hours after elastase instillation; however, the endotoxin-induced decrease reached a nadir 3 to 6 hours after the instillation. Endotoxin induced a significant intraepithelial neutrophil infiltration that peaked 3 to 6 hours after intranasal instillation, coinciding with



A



B

Fig 3. Effects of intraepithelial injection of anti-rat neutrophil antiserum (Anti-N) or cyclophosphamide (CPA) on A) number of circulating total white blood cells and polymorphonuclear cells and B) percent area of mucosubstance in nasal epithelium after elastase instillation. Number of total white blood cells and polymorphonuclear cells significantly decreased in Anti-N- or CPA-treated rats. Elastase-induced epithelial mucus production was not inhibited in these neutrophil-depleted rats ($n = 5$).

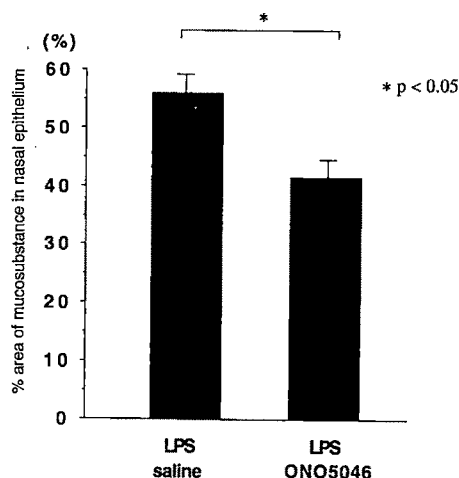


Fig 4. Effects of neutrophil elastase inhibitor ONO-5046 on endotoxin (LPS)-induced epithelial mucus production. Endotoxin-induced mucus production was partially inhibited by intranasal instillation of ONO-5046 (1.5 mg) 1 hour before endotoxin instillation ($n = 6$).

the nadir of the transient decrease of epithelial mucosubstance. Intranasal instillation of elastase did not induce intraepithelial neutrophil infiltration.

DISCUSSION

In this study, intranasal instillation of endotoxin induced intraepithelial mucus production in rat nasal epithelium. A significant increase in the amount of intraepithelial mucosubstance was observed in the nasal septal epithelium after 24 hours during 3 days of endotoxin instillation. The mechanism by which endotoxin causes mucus production is still unclear. It may have a direct effect on epithelial cells, or it may affect the cells indirectly through the inflammatory process. We have observed that intraperitoneal injection of the anti-inflammatory drugs indometha-

cin and dexamethasone significantly inhibits the endotoxin-induced epithelial mucus production.¹¹ These results suggest that epithelial mucosubstance is produced by endotoxin-induced inflammation.

Several studies have recently been reported recognizing the molecular mechanism of endotoxin-induced inflammation. Endotoxin (LPS) binds to LPS-binding protein (LBP), and this LPS-LBP complex binds to CD14 bearing inflammatory cells such as monocytes, macrophages, and neutrophils.¹² The LPS activates the inflammatory process by stimulating the secretion of cytokines (IL-1, IL-6, IL-8, and tumor necrosis factor [TNF]) from macrophages and by activating neutrophil functions.¹³ The LPS-LBP complex also stimulates cytokine production from epithelial and endothelial cells in the presence of soluble CD14.¹⁴ These inflammatory cytokines and inflammatory cells activate the production of inflammatory mediators, which in turn may stimulate the production of epithelial mucus. A variety of inflammatory mediators are capable of stimulating mucus secretion in the airway epithelium. It has been reported that prostaglandins,¹⁵ leukotrienes (LTs),¹⁶ hydroxy-eicosatetraenoic acid,¹⁷ histamine, platelet activating factor, TNF,¹⁸ neuropeptides,¹⁹ proteases released from neutrophils,³⁻⁵ macrophages,²⁰ and bacteria²¹ exert a mucus secretagogue effect on airway epithelial cells.

Neutrophils play an important role in endotoxin-induced mucus production; endotoxin-induced alterations were significantly inhibited in neutrophil-depleted rats. In the present study, intranasal instillation of human recombinant IL-8, which is a strong chemoattractant for rat neutrophils,^{22,23} markedly induced intraepithelial neutrophil infiltration in 2 of

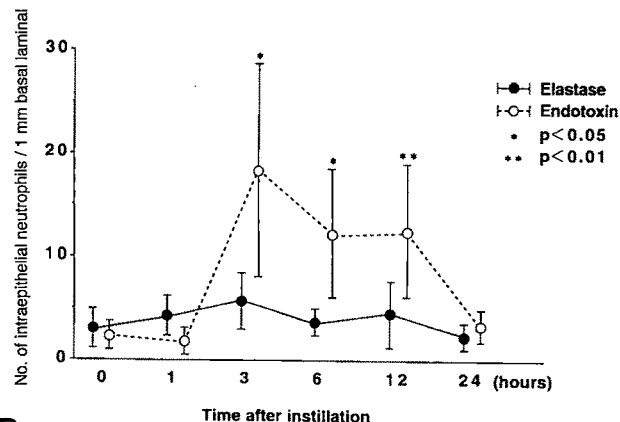
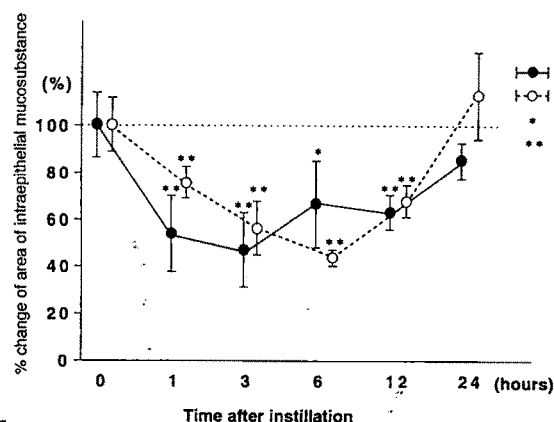


Fig 5. A) Percent changes of area of epithelial mucosubstance and B) number of intraepithelial neutrophils after intranasal instillation of elastase or endotoxin. Transient reduction of epithelial mucosubstance was observed, and it peaked 1 to 3 hours after elastase instillation; endotoxin-induced reduction peaked 3 to 6 hours after instillation, coinciding with peak of epithelial neutrophil infiltration. Elastase did not induce epithelial neutrophil infiltration. Actual percent area of mucosubstance at zero hour was $32.6\% \pm 3.5\%$. Numbers of intraepithelial neutrophils in untreated and saline-instilled controls were 0.5 ± 0.8 and 1.4 ± 1.3 , respectively. Indicated p values are versus zero hour.

the 5 rats examined. The fact that epithelial mucus production was observed only in neutrophil-infiltrating epithelia suggests that neutrophils themselves stimulate epithelial mucus production. The absorption rate of the instilled materials into the nasal mucosa may have been different between animals, because some of the materials are easily removed from the nasal cavity by sneezing and sniffing. This may be the reason why only 2 animals demonstrated neutrophil infiltration after IL-8 instillation.

Neutrophil elastase and other neutrophil proteases play important roles in epithelial mucus production. The intratracheal instillation of neutrophil elastase has induced mucus production and secretory cell metaplasia in hamsters^{3,4} and rats.⁵ The neutrophil elastase inhibitor ONO-5046, developed as a low-molecular weight inhibitor of human neutrophil elastase, has been shown to inhibit rabbit, rat, hamster, and mouse neutrophil elastases.¹⁰ Endotoxin-induced lung injury has been significantly inhibited by ONO-5046 in sheep²⁴ and guinea pigs.²⁵ In the present study, intranasal instillation of elastase induced hypertrophic and metaplastic changes of goblet cells that were similar to those observed after endotoxin instillation. This elastase-induced mucus production was not inhibited in neutrophil-depleted rats; the neutrophil elastase inhibitor ONO-5046 partially inhibited the endotoxin-induced mucus production. These results indicate that neutrophil elastase is an important mediator of endotoxin-induced epithelial mucus production; however, other inflammatory mediators are also probably involved in this change. In a previous study, we showed that intraperitoneal injection of indomethacin (an inhibitor of the cyclooxygenase pathway) partially inhibits endotoxin-induced mucus production,¹¹ but that the cysteinyl LT (LTC₄, LTD₄, and LTE₄) antagonist ONO-1078 did not ef-

fect this change (data not shown). These findings suggest that prostaglandins, but not cysteinyl LTs, mediate endotoxin-induced mucus production.

Changes in the amount of intraepithelial mucosubstance may be affected by the ratio of mucus synthesis to mucus secretion. A transient decrease in epithelial mucosubstance was observed during 12 hours after intranasal instillation of endotoxin or elastase, probably caused by the excess mucus secretion. Mucus synthesis had increased by 24 hours after the instillation, resulting in an increase in the intracellular pool of mucosubstance. Mucus secretion was evaluated by studying this transient decrease in intraepithelial mucosubstance. Harkema et al^{26,27} have reported a transient decrease in the intracellular pool of mucosubstance in the epithelium 6 hours after intranasal instillation of endotoxin in the rat nose. This transient change was not observed in neutrophil-depleted rats.^{26,27} Harkema et al suggested that neutrophils triggered mucus secretion from the epithelial goblet cells after endotoxin instillation. In the present study, time-course changes in the amount of intraepithelial mucosubstance and intraepithelial neutrophil infiltration were compared between endotoxin and elastase instillation. The transient decrease in the intracellular pool of mucosubstance in the epithelium was the lowest 3 to 6 hours after endotoxin instillation, coinciding with the peak of intranasal neutrophil infiltration. On the other hand, the elastase-induced decrease in mucosubstance reached a nadir 1 to 3 hours after the instillation (ie, earlier than the endotoxin-induced change). Elastase did not induce intraepithelial neutrophil infiltration. These results indicate the importance of neutrophil elastase as a direct mediator not only of mucus synthesis, but also of mucus secretion, from the epithelial goblet cells during endotoxin instillation.

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AGE-RELATED DEVELOPMENT OF THE ARRANGEMENT OF CONNECTIVE TISSUE FIBERS IN THE LAMINA PROPRIA OF THE HUMAN VOCAL FOLD

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A scanning electron microscopic study was made on the morphological changes occurring with age in collagen and elastic fibers in the lamina propria of the human vocal fold. We obtained the specimens from 32 autopsy cases ranging from 20 gestational weeks to 22 postnatal years and submitted them to digestion treatments with 10% sodium hydroxide and 90% formic acid. The vocal folds in fetuses and neonates consisted of sparse and dense areas of collagen and elastic fibers, and the vocal ligament was not found. In subjects 5 years of age, a deep dense area was found in the anterior and posterior maculae flavae, and longitudinal fibers were noted between the maculae. A structure of superficial versus deep layers appeared in children older than 10 years of age. The layered structure of the lamina propria was complete around 17 years of age. The development of the layered structure and the maturity of the fibers appeared to reflect the complexity of phonatory function during adolescence.

KEY WORDS — collagen fibers, development, elastic fibers, lamina propria, vocal fold.

INTRODUCTION

The concept of a layered structure of the vocal fold has been established on the basis of a number of studies that suggest that the vocal fold consists of several layers that possess distinct physical characteristics.^{1,2} The most important structure of the vocal fold is the lamina propria, the vibrating part of the larynx. The physical characteristics of the lamina propria are closely related to the courses and distributions of collagen and elastic fibers. However, the developmental changes in vocal fold morphology have rarely been investigated. In particular, electron microscopic studies have not been conducted on subjects over a wide age range.

Scanning electron microscopy (SEM) is a useful method for 3-dimensional analyses of collagen and elastic fibers. The conventional SEM method, however, does not allow precise morphological identification among collagen fibers, elastic fibers, cell components, and interstitial tissue. Collagen fibers contribute to the stability of connective tissue, whereas elastic fibers are related to the resiliency of connective tissue in response to external pressures. To investigate the physical characteristics of 2 kinds of fibers with different functions, one needs precise information on their ultrastructures.

Ishii et al^{3,4} conducted studies on the human vo-

cal fold and reported on the ultrastructures of collagen and elastic fibers. For the observation of collagen fibers, they treated specimens with sodium hydroxide to digest elastic fibers and cellular components. For the observation of elastic fibers, they treated specimens with formic acid to digest collagen fibers and cellular components.⁴

In the present study, the digestion method with sodium hydroxide and formic acid was applied to perform an SEM study on the developmental changes in the lamina propria of the human vocal fold, especially changes in collagen and elastic fibers. This is the first report regarding the age-related changes in ultrastructures of the vocal fold, which were investigated on a large number of autopsy laryngeal specimens at various developmental stages.

SUBJECTS AND METHODS

We examined vocal folds excised from 32 autopsy cases at Kanagawa Children's Medical Center. Table 1 shows background factors (sex, age or gestational weeks, and cause of death) in all cases.

The fetuses had no remarkable anomalies, the neonates were delivered normally (at 37 to 41 gestational weeks) with a body weight of more than 2,500 g, and the infants and children were within the normal limits for height and weight. No external anomalies

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TABLE 1. BACKGROUND FACTORS IN 32 CASES

Case No.	Age	Sex	Cause of Death
1	21-wk fetus		Abortion from early rupture of membrane
2	23-wk fetus		Stillborn child
3	27-wk fetus		Stillborn child
4	28-wk fetus		Stillborn child
5	30-wk fetus		Cytomegalovirus infection
6	0 d	M	Stillborn child
7	0 d	F	Stillborn child
8	0 d	M	Asphyxia neonatorum
9	0 d	F	Asphyxia neonatorum
10	1 d	F	Anomalous pulmonary venous return
11	2 d	F	Prolapse of umbilical cord
12	12 d	M	Pneumonia
13	3 mo	F	Cytomegalovirus infection, pneumonia
14	4 mo	F	Pneumonia
15	5 mo	F	Injury of spinal cord at delivery
16	1 y 3 mo	M	Congenital malformation of heart
17	1 y 8 mo	F	Hepatoblastoma
18	1 y 11 mo	F	Measles pneumonia
19	3 y 0 mo	F	Acute lymphatic leukemia
20	3 y 2 mo	M	Hepatoblastoma
21	3 y 9 mo	M	Congenital malformation of heart
22	5 y 2 mo	F	Cardiomyopathy
23	5 y 9 mo	M	Rhabdomyosarcoma
24	5 y 9 mo	M	Cerebral hypoxia
25	12 y 5 mo	F	Leukemia
26	12 y 6 mo	F	Aplastic anemia
27	12 y 8 mo	M	Liver cirrhosis
28	15 y 2 mo	M	Liver tumor
29	15 y 8 mo	M	Pneumonia
30	16 y 11 mo	M	Brain atrophy
31	17 y 11 mo	M	Sudden death after operation for heart malformation
32	22 y	F	Panperitonitis

or laryngeal diseases were noted. Cases of chromosomal aberration, cerebral palsy, and mental retardation were excluded. All subjects were presumed to have had a normal phonatory development corresponding to their age.

As an adult control group, vocal folds from 10 normal anatomy cases, ranging from 60 to 80 years of age, were also examined.

The posterior surface of each 10% formalin-fixed laryngeal specimen was split open between the arytenoids. The thyroid cartilage, vocal folds, and arytenoids were excised en bloc between the ventricle and subglottis. The vocal folds were then resected in

the longitudinal and lateral directions with a knife.

The digestion method was performed as follows. For observation of collagen fibers, the vocal folds were treated with 10% sodium hydroxide at 37°C for 5 to 7 days after prefixation with 2% glutaraldehyde. The specimens for the observation of elastic fibers were treated with 90% formic acid at 45°C for 1 to 3 days after prefixation with 3% paraformaldehyde.

The specimens were then treated with 1% tannic acid, post-fixed with 1% osmic acid, washed, dehydrated, critical-point-dried, and finally coated with platinum.

The specimens obtained by the above procedures were examined under a scanning electron microscope (Hitachi S-4200).

Sections from some specimens were embedded in Epon. Ultrathin sections were examined under a transmission electron microscope (Hitachi H-7000).

RESULTS

Transmission electron microscopic photographs showed the result from materials of the control group after digestion with 10% sodium hydroxide at 37°C for 6 days for observation of collagen fibers (Fig 1A). Figure 1B shows the result after digestion with 90% formic acid at 45°C for 2 days for the observation of elastic fibers. Both methods revealed good results in demonstrating collagen and elastic fibers, respectively.

In the following SEM photographs, the thyroid cartilage is located on the left, the arytenoid cartilage on the right, the mucosal epithelium on the top, and the muscle layer on the bottom.

Collagen Fibers. In the fetuses at 30 gestational weeks and less, in the central superficial part, collagen fibers were distributed rather sparsely, whereas they were dense in the anterior, deep, and posterior parts of the lamina propria. Under high magnification, thin fibers (about 1 μ m in diameter) of a slightly low density were found running in random directions in the central superficial part. In the anterior, deep, and posterior parts, thin coiled fibers were intertwined tightly and densely.

In neonates, the lamina propria consisted of a sparse area in the central superficial part and a dense area in the anterior, deep, and posterior parts (Fig 2). Although the sparse area in the superficial part had increased in thickness compared with that in fetuses, the fibers ran at random and no longitudinal arrangement was found. Thin fibers were distributed abundantly in the deep, anterior, and posterior parts.

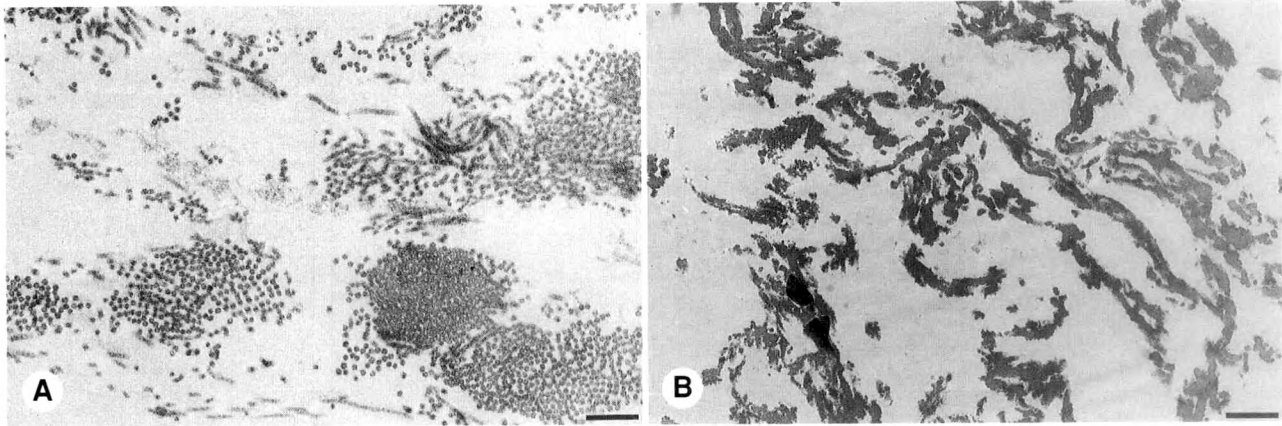


Fig 1. Control specimens. A) Collagen fibers after digestion with 10% sodium hydroxide. Scale bar — 0.3 μm . B) Elastic fibers after digestion with 90% formic acid. Scale bar — 1 μm .

In the 5-month-old infant, in the central superficial part, some thin collagen fibers were arranged longitudinally in the sparse area (Fig 3).

In the 1-year-old children, in the central superficial part, collagen fibers revealed that the sparse area was increased in thickness. The longitudinal arrangement of fibers was clearly distinguished just under the mucosal epithelium. The dense area was continuous in the anterior, deep, and posterior parts. In the anterior part, slightly separated from the thyroid cartilage, thin fibers (about 1 μm in diameter) were intertwined tightly and randomly, having a massive structure. In the posterior part, slightly thicker fibers (about 3 μm in diameter) were directly connected to the arytenoid cartilage in a fashion similar to that of the anterior and posterior maculae in adults.

In the 3-year-old children, collagen fibers were found running longitudinally in a wide range of the vocal fold, from the mucosal epithelium to the deep part adjacent to the muscle layer. In the deep part, fibers formed several masses, although these masses were separated from the anterior and posterior maculae. Under higher magnification, mostly linear fibers (about 2 μm in diameter) showed a markedly longitudinal arrangement in the superficial part. The density of fibers increased slightly. The superficial layer, which was found in older children and adults, was not identifiable under the epithelium (Fig 4A). In the deep part, thin fibers were intertwined densely in random directions (Fig 4B).

In the 5-year-old children, a longitudinal arrangement of collagen fibers (about 2 μm in diameter) was

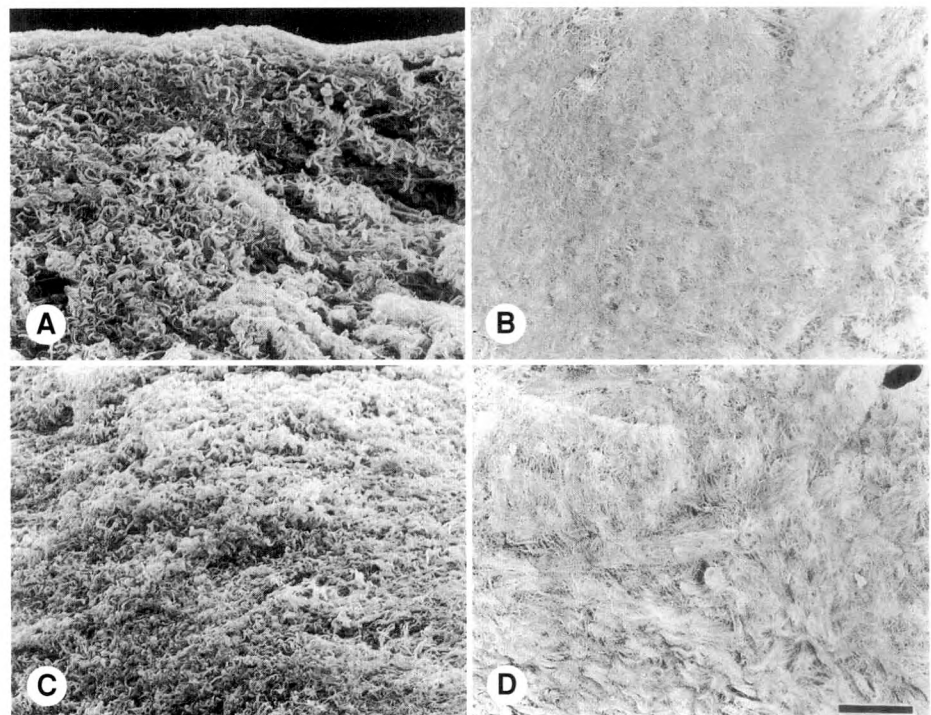


Fig 2. Collagen fibers in neonate. Scale bar — 40 μm . Distribution of fibers was sparse in A) superficial part and dense in B) deep part, C) anterior part, and D) posterior part.

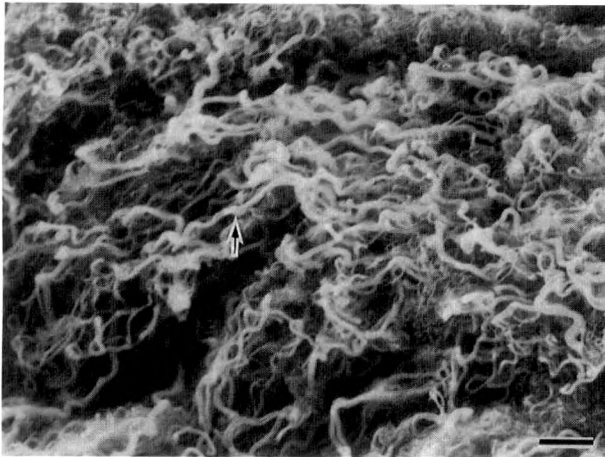


Fig 3. Collagen fibers in 5-month-old infant. Highly magnified view of superficial part. Scale bar — 20 μ m. Some fibers showed longitudinal arrangement (arrow).

found in all layers of the lamina propria. Dense masses, which were found just above the muscle layer in the 3-year-old children, were not found. The superficial layer was not identifiable under the mucosal epithelium. Under high magnification, longitudinal fibers showed a curvature (Fig 5).

In the 12-year-old children, in the superficial part, coiled thin fibers (about 0.5 μ m in diameter) were distributed sparsely. The superficial layer was identifiable (Fig 6A). In the intermediate layer, longitudinal fibers (about 2 μ m in diameter) in bundles showed curvature and an increase in density (Fig 6A). In the deep part, thin fibers showed an irregular arrangement running in random directions (Fig 6B).

In the 17-year-old children, in the superficial layer, thin coiled fibers (about 0.5 to 1 μ m in diameter) were intertwined irregularly. Furthermore, small nodular structures, which were also observed in adults, were noted (Fig 7A). Compared with the 12-year-old children, thick longitudinal fibers (about 10 μ m in diameter) in the intermediate layer were increased in diameter and showed more linear-running courses due to decreases in curvature (Fig 7B). In the deep layer, which was differentiated from the intermediate layer, thin fibers were distributed irregu-

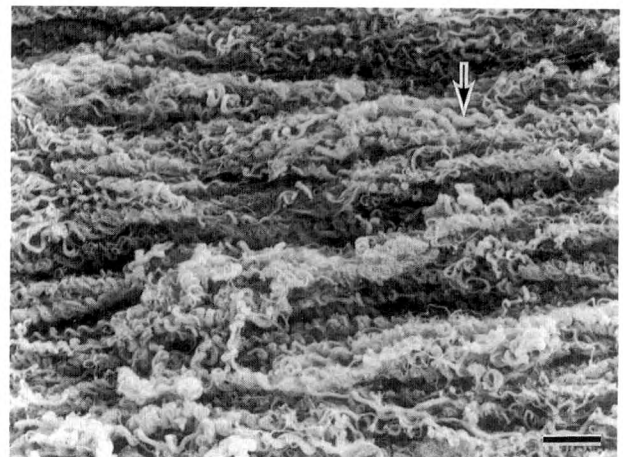


Fig 5. Collagen fibers in 5-year-old child. Scale bar — 20 μ m. Uniform fibers were distributed in all layers. Longitudinal fibers showed curvature (arrow).

larly in random directions (Fig 7C).

In the 22-year-old woman, the diameter and curvature of curled collagen fibers in the intermediate layer were the same as we observed in the 12-year-old children (Fig 7D). The diameter of collagen fibers in the intermediate layer tended to be greater in men than in women after adolescence.

Elastic Fibers. In the fetus at 30 gestational weeks, in the central superficial part, thick elastic fibers (about 6 μ m in diameter) were distributed rather sparsely, running in random directions. The longitudinal arrangement of the ligament, which appeared at a later stage of development, was not yet found (Fig 8A). In the anterior, deep, and posterior parts, thin elastic fibers (about 2 μ m in diameter) were dense (Fig 8B-D).

In the neonates, thick elastic fibers were found running at random in the sparse area in the central superficial part (Fig 9A). Thin elastic fibers were abundant in the deep part (Fig 9B).

In the 5-month-old infant, although the sparse superficial part was increased in thickness, the deep part was dense and continuous to the anterior and posterior parts. In the central superficial part, thick

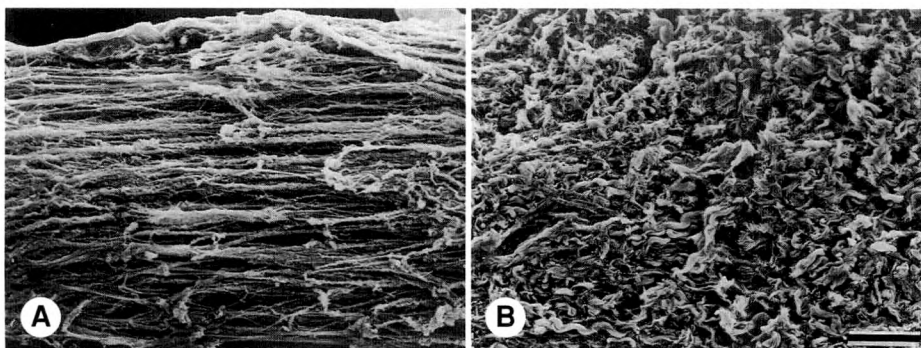
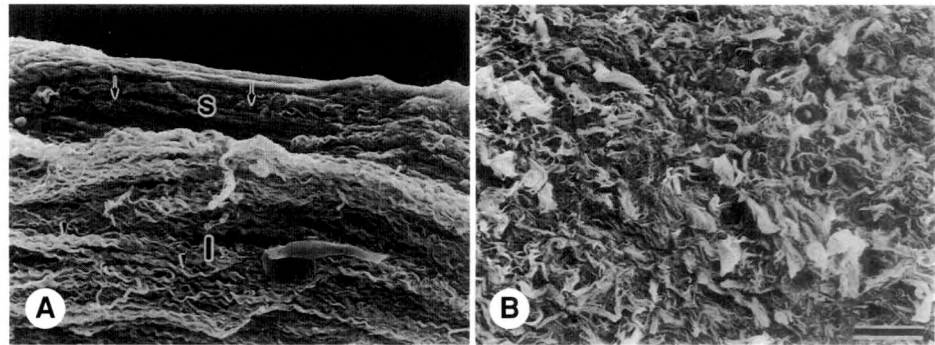


Fig 4. Collagen fibers in 3-year old child. Scale bar — 50 μ m. A) Superficial part. Longitudinal fibers were found running just under mucosal epithelium. B) Deep part.

Fig 6. Collagen fibers in 12-year-old child. Scale bar — 40 μ m. A) Superficial and intermediate layers. Thin coiled fibers (arrows) were distributed sparsely in superficial layer (S). Large curly fibers (arrowheads) were found in intermediate layer (I). B) Deep layer. Arrangement of fibers was irregular in deep layer.



fibers were distributed sparsely, and some showed a longitudinal arrangement (Fig 10A). Thin fibers were abundant in the deep part (Fig 10B).

In the 1-year-old children, elastic fibers exhibited a sparse longitudinal arrangement in the central superficial part. The dense area in the deep part had a massive appearance, although it was decreased in thickness. The dense area in the anterior and posterior parts tended to be separated from the dense area in the deep part. These areas formed markedly dense fibrous masses, which were considered to be the anterior and posterior maculae.

In the 3-year-old children, in the superficial part, longitudinal fibers increased in density. The running direction of the fibers was random in the deep part.

In the 5-year-old children, elastic fibers with a uniform appearance independent of location were distributed in a longitudinal arrangement. Under high magnification, bundles of linear fibers (about 4 to 6 μ m in diameter) were entwined by thin coiled fibers in random directions (Fig 11). The same condition

was found just above the muscle layer. The dense area, which was found in the 3-year-old children, was not found.

Under light microscopic observation, specimens from the 5-year-old children showed increases in the number of collagen fibers in the intermediate and deep areas. Differences in fiber density were noted among the layers. However, upon SEM observation of the same specimens, morphological differences were not found among fibers located in each layer.

In the 12-year-old children, the density of the elastic fibers was sparse, and thin coiled fibers ran irregularly in the superficial part (Fig 12A). In the intermediate layer, thick longitudinal fibers were increased in diameter and showed branching (Fig 12B). In the deep part, thin coiled fibers (about 2 to 3 μ m in diameter) were densely distributed, running in random directions (Fig 12C).

In the 17-year-old children, the superficial layer containing thin coiled fibers was differentiated (Fig 13A). In the intermediate layer, branching of longi-

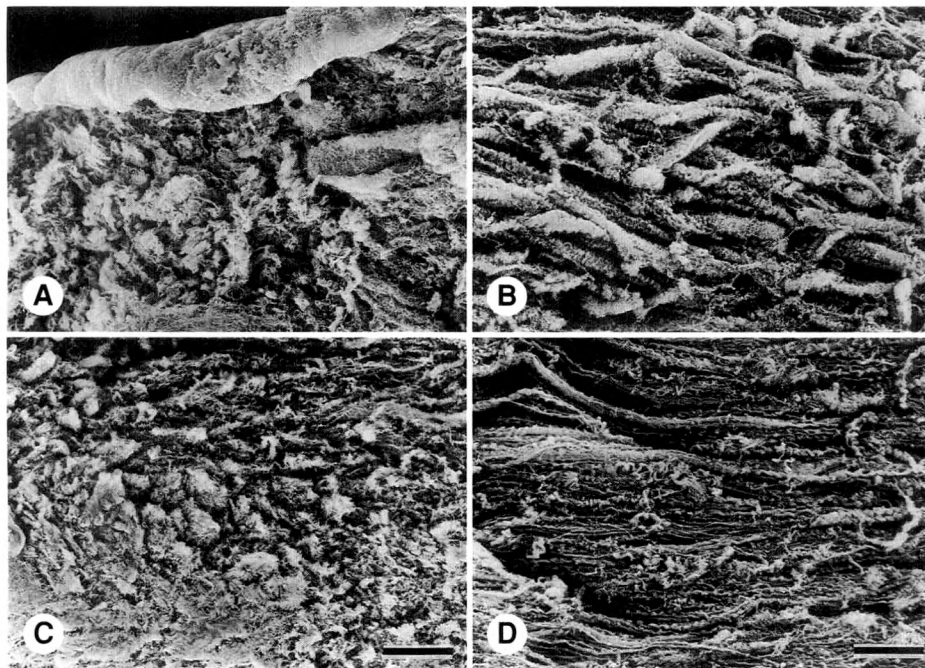


Fig 7. Collagen fibers after adolescence. Scale bar for A and C is 100 μ m; that for B and D is 50 μ m. A) Superficial layer in 17-year-old boy. Thin fibers formed small nodular structures. B) Intermediate layer in 17-year-old boy. Longitudinal fibers increased in diameter and ran more linearly. C) Deep layer in 17-year-old boy. Thin fibers were intertwined in random directions. D) Intermediate layer in 22-year-old woman. Longitudinal fibers, with diameter similar to that of preadolescent subjects, showed curvature.

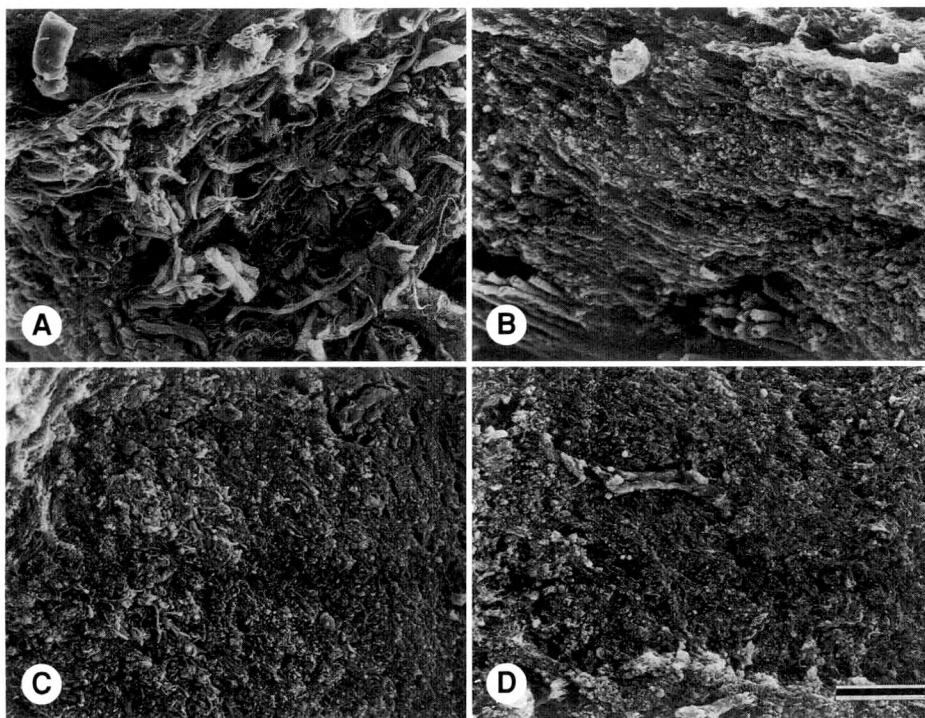


Fig 8. Elastic fibers in fetus at 30 gestational weeks. Scale bar — 40 μ m. A) Superficial part. Fibers were sparse and randomly distributed. B) Deep part. C) Anterior part. D) Posterior part. Fibers were dense except in superficial part.

tudinal fiber bundles was more marked (Fig 13A). Although the deep layer, similar to the superficial layer, contained thin coiled fibers, the longitudinal fibers were more predominant compared to those of adults (Fig 13B).

Figure 14 shows a schematic drawing of the developmental changes in the vocal fold lamina propria based on the findings in the present study. The results may be summarized as follows.

1. In fetuses and neonates, the lamina propria consisted of a dense area (d in Fig 14A) in the anterior, deep, and posterior parts and a slightly sparse area (s in Fig 14A) in the central superficial part. A longitudinal arrangement of fibers was not found.

2. In infants and 1-year-old children, the dense area was separated into the anterior (asterisk in Fig 14) and posterior maculae. The longitudinal fibers (l in Fig 14A) were found between the maculae in the superficial part.

3. In 3-year-old children, the longitudinal fibers in the central part were increased in number. Differentiation of the superficial layer was not found under the mucosal epithelium.

4. In 5-year-old children, longitudinal curly collagen fibers (lcc in Fig 14B) and linear elastic fibers (le in Fig 14B) were found in all layers of the vocal fold lamina propria. The fibers were uniform, irrespective of the depth of their location. Differentia-

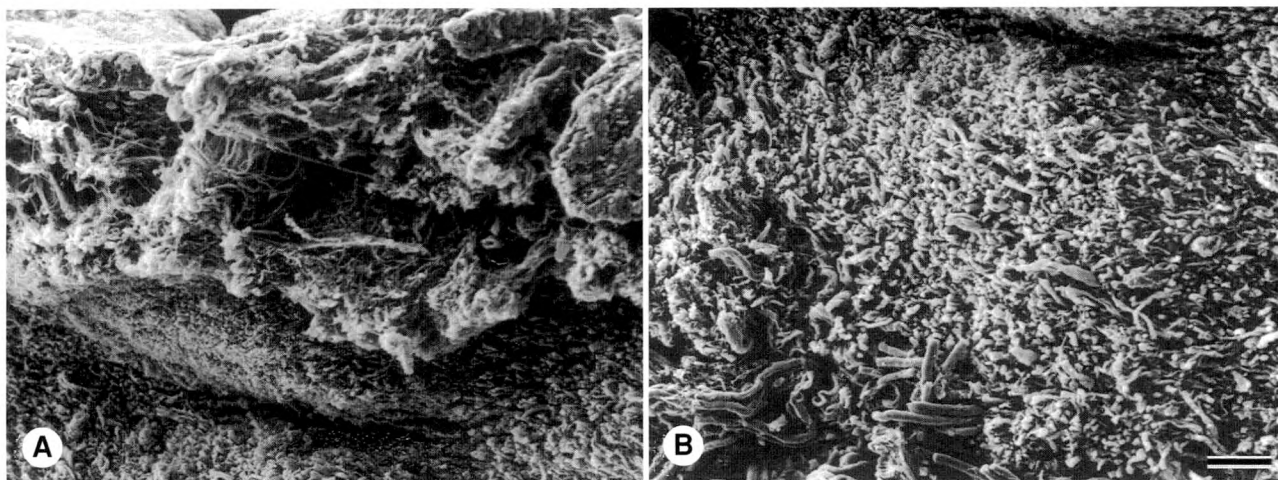
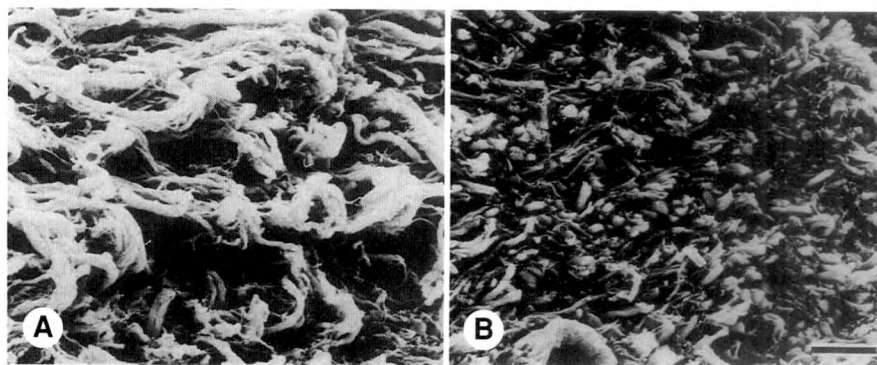


Fig 9. Elastic fibers in neonate. Scale bar — 20 μ m. A) Superficial part. Fibers were sparse and randomly distributed. B) Deep part.

Fig 10. Elastic fibers in 5-month-old infant. Scale bar — 20 μ m. A) Superficial part. Slightly larger fibers ran in longitudinal direction. B) Deep part.



tion of the superficial and deep layers was not found.

5. In 12-year-old children, thin coiled collagen and elastic fibers were located in the superficial layer. Slightly large collagen fibers and thin coiled elastic fibers were found running in random directions in the deep layer. The intermediate layer was identifiable because of the characteristics of fibers running therein.

6. In 17-year-old children, differentiation of the superficial and deep layers was more evident. The appearance was close to that of the layered structure of adult vocal folds.

7. Elastic fibers in the intermediate layer increased in diameter and branching with age.

8. Collagen fibers in the intermediate layer showed a curlier appearance with age.

9. Collagen fibers in the intermediate layer decreased in curvature and increased in diameter only in males after adolescence.

DISCUSSION

Fetuses and Neonates. Wind⁵ reported that vocal

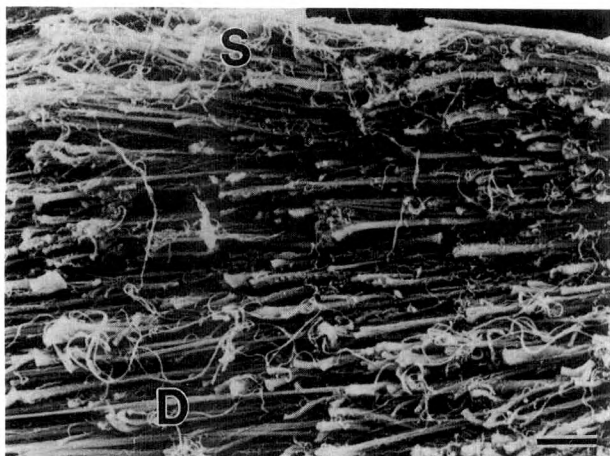


Fig 11. Elastic fibers in 5-year-old child. Scale bar — 20 μ m. Uniform fibers were distributed from superficial part (S) just under mucosal epithelium to deep part (D) just above muscle layer.

fold development occurs late in comparison to other structures in the larynx, such as cartilage and muscles. The lamina propria was found to consist of sparse and dense areas in fetuses and neonates. This structure was markedly different from that in older children. Hirano¹ and Kurita² reported that the lamina propria had a uniform appearance under the light microscope at this developmental stage. Upon observation with SEM, the central superficial part may have appeared sparse because this part was abundant in cellular components that were digested by the treatment. However, the shape and structure of collagen and elastic fibers were apparently different in the sparse and dense areas. It was determined that the lamina propria consisted of 2 areas, sparse and dense, in fetuses and neonates. This sparse-dense structure might be an immature preparatory condition, which would be changed or absorbed later and replaced by a more developed structure consisting of the ligament and macula flava.

Infants and 1-Year-Old Children. At this stage, the sparse-dense structure found in fetuses and neonates changed into a structure in which the anterior and posterior maculae were differentiated from the deep dense area. Longitudinal fibers were observed in the sparse area between these maculae. Longitudinal fibers, the fundamental component of the future ligament, were produced by fibroblasts in the macula flava. From the findings of the present study, we speculated that the macula flava was differentiated from the deep dense part. Longitudinal fibers in the macula flava are produced by growth-related endocrine stimuli and mechanical stimuli such as crying and babbling. At the speaking stage, the number of longitudinal fibers increases and the fundamental structure of the vocal ligament is completed.

Children Between 3 and 5 Years of Age. The dense deep part was decreased in thickness and the longitudinal fibers in the superficial part were increased in number in the 3-year-old children. In the 5-year-old children, longitudinal uniform fibers were found throughout the lamina propria between the mucosa

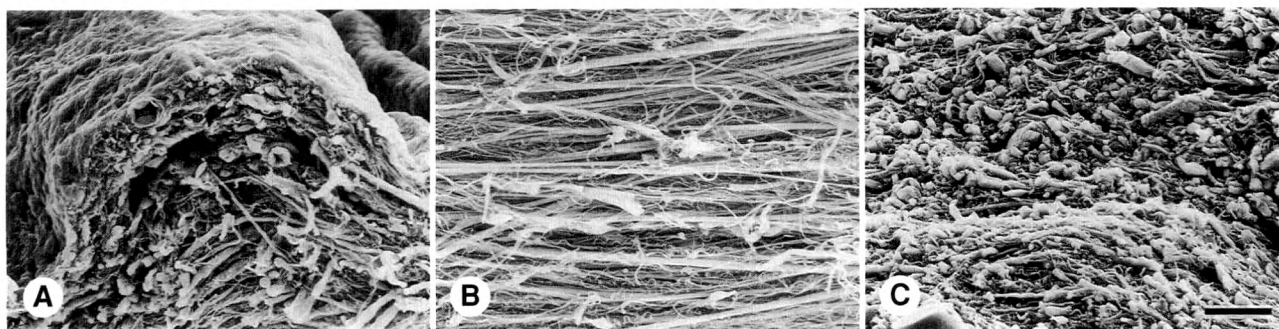


Fig 12. Elastic fibers in 12-year-old child. Scale bar — 40 μ m. A) Superficial layer. Coiled fibers were distributed sparsely. B) Intermediate layer. Longitudinal fibers showed branching. C) Deep layer. Fibers ran in random directions.

and the muscle. At 5 years of age, the layered structure was not found on SEM observation. The most notable finding was the absence of the superficial layer. Longitudinal fibers were distributed under the mucosal epithelium. Collagen and elastic fibers showed differences in morphology from those of the ligament in adult vocal folds. It was determined that the superficial layer plays an important role in the maintenance of regular vibration of the vocal fold.

In the period from 5 to 10 years of age, phonatory activity increases markedly and rapidly. Mechanical stress to the vocal fold is expected to be severe because of the lack of the superficial layer. This period corresponds to the period of so-called pediatric hoarseness. Although the vulnerability and susceptibility of the vocal folds are mainly attributable to vascular immaturity, the immature structure of the vocal fold lacking the superficial layer is also considered to be an important cause. Voice abuse induces an overload of the lamina propria and produces an edema or nodule in the vocal fold that lacks the superficial layer.

Twelve-Year-Old Children. The differentiation of

the superficial and deep layers was found to occur in the teens. Thin coiled elastic fibers appeared in the superficial layer. This change might facilitate mucosal waves in the superficial layer, because of the increase in mobility or flexibility of the lamina propria. After mucosal wave movement during phonation, the lamina propria returns to the resting position quickly because of its elasticity. Thin collagen fibers were also increased in density. In adults, collagen fibers exhibited a nodular distribution. This change might be useful for preventing the deviation of vocal fold contents during mucosal waves, sustaining the layered structure, and keeping mucosal waves stable. These findings are adaptive changes to the development of phonatory function, especially the variety of mucosal waves.

Coiled collagen fibers increased in density in the deep layer, which might facilitate changes in vocal fold thickness corresponding to the contraction and relaxation of the internal muscle. Collagen fibers running in random directions also increased in density in the deep layer. The fundamental structure of the vocal fold might be preserved by this change in the deep layer, which probably reduces the mechanical

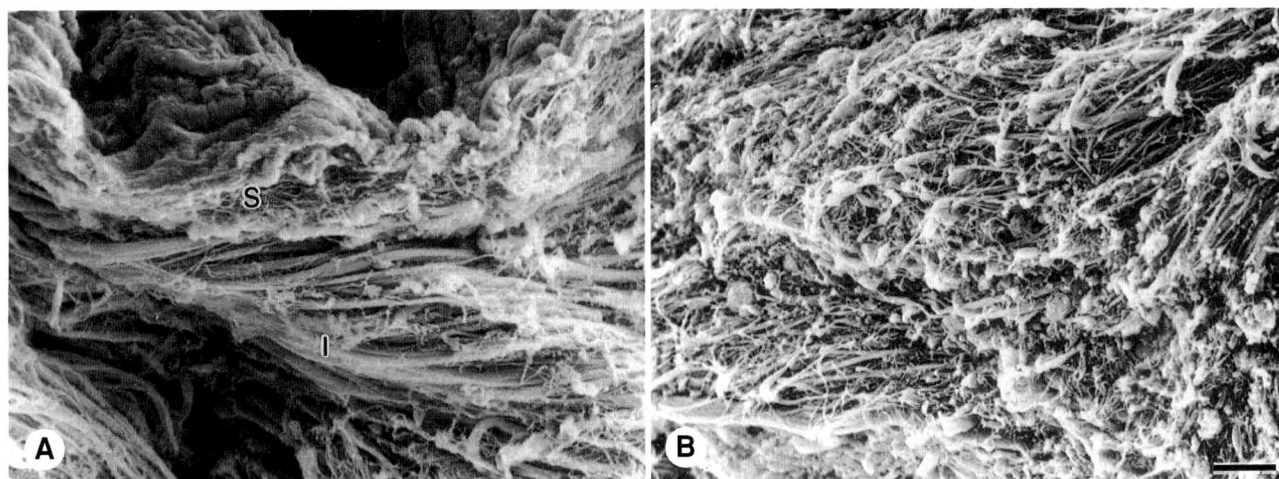


Fig 13. Elastic fibers in 17-year-old boy. Scale bar — 20 μ m. A) Superficial and intermediate layers. Superficial layer (S) with sparse density was found just under mucosal epithelium. Branching of fibers was noted in intermediate layer (I). B) Deep layer.

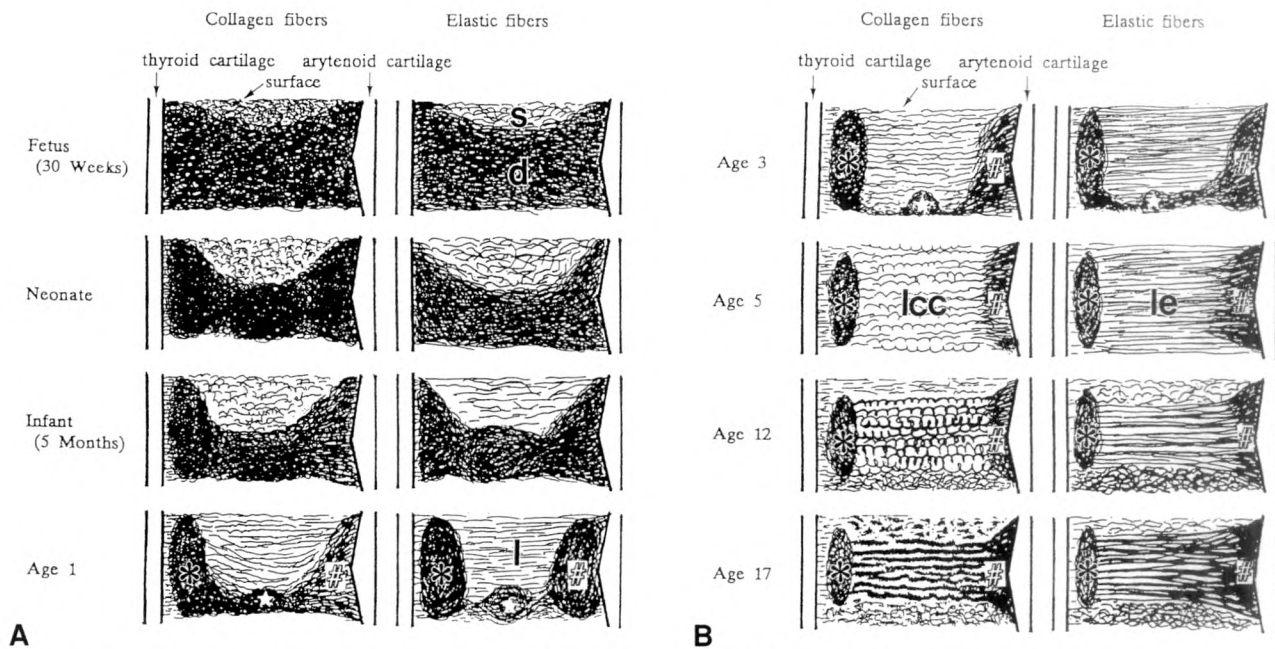


Fig 14. Developmental changes in lamina propria of human vocal fold. A) Infants. B) Ages 3 and up. Lamina propria showed sparse-dense structure in fetuses and neonates. Both collagen and elastic fibers had longitudinal arrangement at age of 1 year. Longitudinal collagen fibers showed increased curvature with age. Diameter of longitudinal fibers increased rapidly in 17-year-old boy. Longitudinal elastic fibers increased in branching with age. Differentiation of superficial and deep layers progressed in terms of collagen and elastic fibers after age of 12 years. Asterisk — anterior macula flava; # — posterior macula flava; star — vestige of deep part; d — dense area; s — sparse area; l — longitudinal fibers; lcc — longitudinal curly collagen fibers; le — linear elastic fibers.

effects of the internal muscle on the mucosa and lamina propria. The above differentiation of the deep layer was considered to be adaptive to the development of phonatory function, especially the complicated regulation of the larynx.

In children older than 10 years of age, maturation of fibers in the intermediate layer was observed along with the differentiation of the layered structure. Collagen fibers in the intermediate layer increased in diameter and branching. The increases in diameter and branching might be related to the quick and diverse regulation of the larynx.

On the other hand, the collagen fibers in the intermediate layer gradually increased in curvature. Collagen fibers, consisting of collagen as the main component, bear strong tension. Collagen fibers, which run parallel to elastic fibers in the intermediate layer, are considered to respond to a strong force to the longitudinal direction.⁴ The curvature of fibers first found in young children exhibited a typical appearance in children older than 10 years of age. This curvature might be a structure responding to tension on the vocal fold, although the details are unknown.

After Adolescence. The curly collagen fibers in the intermediate layer decreased in curvature only in males after adolescence. The course of the fibers was more linear, and the diameter of the fiber bundles increased rapidly. The relationship between the above

changes and voice mutation is unknown.

Characteristic findings during voice mutation in males are increases in the anterior-posterior axis of the larynx, increases in the length of the vocal fold, and changes in vocal pitch.⁶ A decrease in the voice frequency occurs because of the elongation of the vocal fold. However, it is still controversial whether the rapid change in pitch during voice mutation is exclusively caused by elongation of the vocal fold.^{7,8}

The decrease in curvature of the fibers was considered to be a passive change that occurred in conjunction with the rapid increase in vocal fold length during adolescence. However, it should be investigated whether changes in the lamina propria, for example, changes in the course and diameter of the collagen fibers, affect the tonus and density of the vocal fold.

Relationship Between Morphological Change and Development in Phonatory Function. Table 2 shows the relationship between the changes in the lamina propria and development of phonatory function and language.

In fetuses without phonation, the development of the vocal fold was delayed in comparison to other structures in the larynx. The lamina propria in neonates had an immature sparse-dense structure lacking longitudinal fibers or ligaments.

TABLE 2. MORPHOLOGICAL CHANGES OF VOCAL FOLD AND DEVELOPMENT OF PHONATORY FUNCTION

	<i>Development of Lamina Propria of Vocal Fold</i>	<i>Development of Phonation and Speech</i>
Fetuses, neonates	Immature sparse-dense structure lacking longitudinal fibers	Without phonation
Infants to age 1	Production of longitudinal fibers; differentiation of macula flava	Crying, babbling
Ages 3-5	Increase of longitudinal fibers; undifferentiation of superficial layer	Fundamental phonation (hoarseness in children)
Age 12	Differentiation of superficial and deep layers; maturity of fibers in intermediate layer	Complexity of phonatory function
Ages 15-17	Changes in collagen fibers in males	Voice mutation

The anterior and posterior maculae were differentiated in infants and 1-year-old children. Crying stimuli after birth might elicit the production of longitu-

dinal fibers between the maculae. This period might be a preparatory period for producing the vocal fold ligament.

In the period from 3 to 5 years of age, longitudinal fibers increased in number. The intermediate layer had an almost mature ligament appearance similar to that in adults. Because of this structure, children in this period can perform fundamental phonation. However, the superficial layer was not differentiated. The immature layered structure of the vocal fold is probably responsible for the susceptibility to pediatric hoarseness.

Differentiation of the superficial and deep layers was noted in children older than 10 years of age. Fibers in the intermediate layer were also mature. The development of the layered structure and the maturity of fibers reflect the complexity of phonatory function in this period.

The development of the lamina propria in males is considered complete after changes in collagen fibers occur in adolescence.

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LARYNGEAL HISTOLOGIC FINDINGS IN INFANTS WITH PALATAL DEFECTS WITH OR WITHOUT CRANIOFACIAL MALFORMATIONS

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The objective of this study was to determine whether specimens from infants with palatal defects (PDs) with or without craniofacial malformations (CFMs) exhibit aberrant laryngeal histologic findings compared with specimens from normal infants. Ten laryngeal specimens from infants with PDs with or without CFMs were histologically compared with 7 laryngeal specimens defined as normal from the same collection. Both groups were similar in terms of demographics and airway manipulation. All infants were prelingual. Comparisons were made at 3 levels: supraglottic, glottic, and subglottic. Histologically, no significant differences in primary laryngeal structures were found between the PD with or without CFM group and the group defined as normal. Acquired and intubation-type injuries, such as inflammation, ulceration, capillary congestion, and scar tissue, were more prevalent and severe in the study group. The primary laryngeal histologic findings of specimens from individuals with PDs with or without CFMs do not differ substantially from those from normal individuals; however, individuals with PDs do appear to be somewhat more susceptible to intubation injury and other acquired laryngeal injury. Meticulous airway management is essential.

KEY WORDS — craniofacial malformations, histology, larynx, palatal defects.

INTRODUCTION

The literature suggests a relationship between palatal deformities, either in isolation or as part of a syndrome, and laryngeal dysfunction. The origin of this laryngeal dysfunction is unknown. Most authors have assumed that abnormal velopharyngeal valving, regardless of clefting, results in respiratory and laryngeal compensations that lead to the development of abnormal voice production.¹⁻⁴ Reports of the concomitant presentation of resonance and voice disorders question this cause-and-effect relationship.⁵ Although several authors have described laryngeal anatomy, function, or both in individuals with palatal defects (PDs),³⁻⁷ few studies have examined infants before the development of speech (Zarzur and Olival Costa, unpublished observations). No study has described the laryngeal histologic findings of specimens from infants with PDs. The goal of this study was to determine whether specimens from patients with PDs with or without craniofacial malformations (CFMs) exhibit aberrant laryngeal histologic findings compared with specimens from normal individuals.

MATERIALS AND METHODS

We reviewed 10 laryngeal specimens from infants with PDs with or without CFMs (study group; Table 1) and compared them with 7 laryngeal specimens

TABLE 1. STUDY GROUP

Specimen No.	Sex	Age	Diagnosis	Airway Manipulation
1	F	19 WG	CL, SCP	None
2	F	3 d	GS, HPP	None
3	M	1.5 mo	CP, MIC	Intubation (30 d)
4	F	2 mo	PRS	Intubation (36 d)
5	M	3 mo	CLP	Intubation (18 d)
6	M	4 mo	MS, HPP	Intubation (7 d)
7	M	6 mo	PRS	Tracheostomy (6 mo)
8	F	6 mo	SCP	Intubation (30 d), tracheostomy
9	F	7 mo	PRS	Intubation (3 d), tracheostomy
10	M	1 y	CLP, MIC	Intubation (7 d), tracheostomy

WG — weeks of gestation; CL — cleft lip; SCP — submucosal cleft palate; GS — Goldenhar's syndrome; HPP — high peaked palate; CP — cleft palate; MIC — micrognathia; PRS — Pierre Robin sequence; CLP — cleft lip and palate; MS — Mohr syndrome.

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TABLE 2. CONTROL GROUP

Specimen No.	Sex	Age	Airway Manipulation
1	M	1 d	None
2	M	1 d	Intubation (1 d)
3	F	1 d	Intubation (1 d)
4	M	2 mo	Intubation (40 d)
5	F	4 mo	Intubation (3 mo), tracheotomy
6	M	6 mo	None
7	M	18 mo	None

from patients without any palatal, craniofacial, or upper airway malformations (control group; Table 2). All infants from both groups were essentially prelingual. All specimens were from the collection of the Laryngeal Development Laboratory at the Children's Memorial Hospital in Chicago, Illinois. The study and control groups were compared with normal specimens (see Figure) from the collection, as well as with normal specimens described by Hirano and Sato.⁸

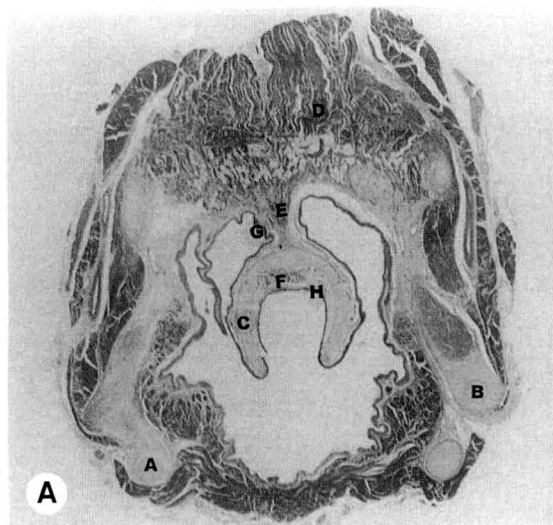
The specimens from both groups were prepared as horizontal whole organ serial sections in the man-

ner described by Tucker et al.⁹ The larynges were obtained at postmortem examination in a conventional manner. Most specimens included the entire hyoid bone superiorly, 2 or more tracheal arches inferiorly, and hypopharyngeal mucosa posteriorly. The block of tissue was kept intact, unsplit, and fixed in 10% buffered formalin. After decalcification and dehydration, the block was embedded in pyroxylin and serially sectioned at 26 to 28 μ m in the horizontal plane from top to bottom. Every 20th section was mounted and stained in hematoxylin and eosin.

Comparisons were made at 3 levels: 1) supraglottic, in which the epiglottic shape could be examined in its entirety; 2) glottic, in which the entire length of the vocal cords could be seen; and 3) subglottic, with the whole cricoid ring as a reference.

RESULTS

As seen in Tables 1 and 2, the study and control groups were essentially homogeneous in terms of demographics and airway manipulation. In the study group, the mean age was 4.5 months, and 80% had



Normal laryngeal histologic findings. A) Supraglottis. A — superior cornu of thyroid cartilage; B — thyroid lamina; C — epiglottic cartilage; D — tongue muscles; E — glossoepiglottic fold; F — preepiglottic space with fibroblasts and fat; G — stratified epithelium at free edge of epiglottis; H — columnar ciliated epithelium at posterior surface of epiglottis. B) Glottis. A — thyroid cartilage; B — cricoid cartilage; C — arytenoid cartilage; D — thyroarytenoid muscle; E — posterior cricoarytenoid muscle; F — squamous stratified epithelium at intramembranous portion of vocal folds; G — pseudostratified ciliated epithelium at intercartilaginous portion of vocal folds. C) Subglottis. A — cricoid cartilage; B — laryngeal glands throughout mucosa.

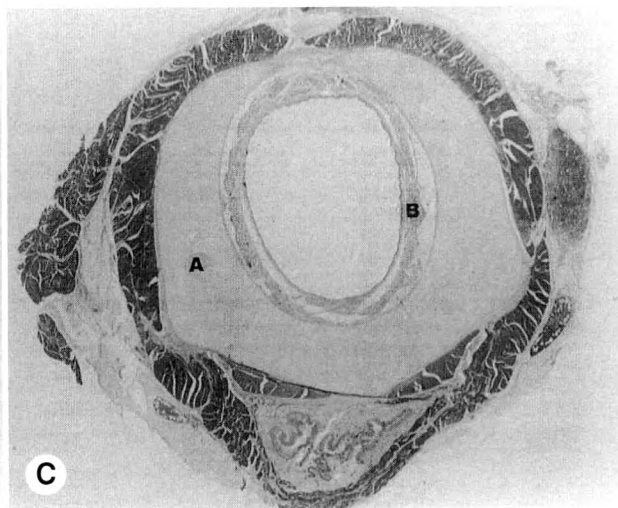
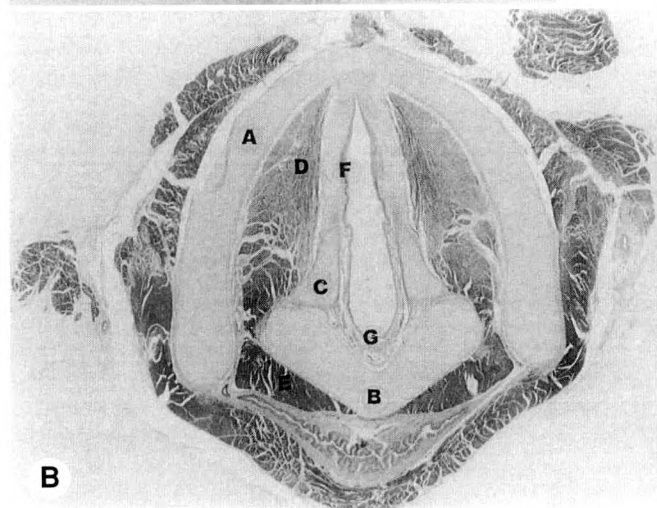


TABLE 3. STUDY GROUP FINDINGS

<i>Specimen No.</i>	<i>Findings</i>
1	Normal
2	Rudimentary epiglottis
3	Thickening of cricoid ring mucosa with fibrous tissue and atrophic glands
4	Glottic: increased dilated submucosal glands; subglottic: capillary hyperplasia and lymphangiectasia
5	Supraglottic: dilated submucosal glands, mild inflammation; glottic: moderate perichondritis, moderate degree of ulceration at vocal process of arytenoids; subglottic: increased submucosal glands with mucosal thickening, lymphangiectasia, moderate perichondritis
6	Rudimentary epiglottis
7	Supraglottic: increased submucosal glands, mild inflammation; glottic: posterior scar tissue, fibrosed areas of ulceration; subglottic: capillary congestion with mild inflammation
8	Glottic: increased submucosal glands at anterior commissure; glottic and subglottic: increased keratinized squamous epithelium and capillary proliferation
9	Glottic and subglottic: increased dilated submucosal glands
10	Normal

manipulation of the airway. Of the 10 individuals, 5 required intubation alone, 2 required tracheostomy after intubation, and 1 required tracheostomy alone. The mean duration of intubation was 44.2 days. In the control group, the mean age was 4.2 months, and 57% had manipulation of the airway. Of these 7 individuals, 3 required intubation alone, and 1 required tracheostomy after intubation. The mean duration of intubation was 33 days. As best as could be ascertained from the patients' records, none of the infants in either group had acquired actual speech.

Although both groups were similar in terms of demographics and airway manipulation, the infants with PDs with or without CFMs exhibited a higher prevalence and increased severity of acquired laryngeal injury when histologically compared with the control group (Tables 3 and 4). The acquired injuries (capillary congestion, lymphangiectasia, ulceration, perichondritis, and scar tissue) were seen in 5 of 10 individuals in the study group, compared with 1 of 7 individuals in the control group. All individuals with such findings had a history of intubation, tracheostomy, or both.

Other congenital anomalies were observed in 2 individuals in the study group and no individuals in the control group. A rudimentary epiglottis was observed grossly at autopsy in 2 individuals with established syndromes (Goldenhar's and Mohr syndromes) asso-

TABLE 4. CONTROL GROUP FINDINGS

<i>Specimen No.</i>	<i>Findings</i>
1	Glottic: mild submucosal gland dilation
2	Normal
3	Normal
4	Glottic (posterior): dilated submucosal glands, mild capillary congestion, bacterial colonies
5	Glottic: mild submucosal gland dilation
6	Normal
7	Normal

ciated with CFMs. Grossly, the epiglottis had a small, malformed appearance, but the underlying histologic composition was unremarkable. Only 1 previous case of a supraglottic or laryngeal anomaly (hemihypertrophic epiglottis seen on laryngoscopy in a patient with Goldenhar's syndrome⁶) has been reported in association with either of these syndromes. No significant differences in cartilage structure, muscle distribution, or epithelial composition were noted between the 2 groups.

Other findings, such as increased or dilated submucosal glands, are not well understood. Increased and/or dilated submucosal glands were seen in similar numbers (5 of 10 in the study group, 3 of 7 in the control group) and of similar severity in both groups, including some patients with no history of airway trauma. The significance, if any, of such a finding is yet to be determined.

DISCUSSION

Perhaps the major finding of this study is the relative lack of significant differences in the laryngeal histologic findings of our study and control groups. Although the specimens from the 2 infants with established CFMs (1 with Goldenhar's syndrome, 1 with Mohr syndrome) demonstrated a grossly rudimentary epiglottis, no significant congenital histologic differences were noted. The fundamental histologic similarity between the 2 groups lends support to the acquired-compensatory theory rather than to the theory of a congenital origin of abnormal voice production. Although all infants in both groups were technically prelingual, prior studies have demonstrated that laryngeal function starts early in gestation.¹⁰ Therefore, infants could develop "compensatory" changes in laryngeal structure and function even before birth.

Interestingly, although similar in terms of demographics and airway manipulation, the study group exhibited a greater propensity for acquired injury than the control group. This is the first study to demonstrate an increased risk of acquired laryngeal trauma in infants with PDs. Although the reason for this increased risk is not established, personal experience

would suggest that increased difficulty of laryngeal visualization during laryngological procedures, as well as presumed aberrant endotracheal tube positioning arising from PDs with or without CFMs, may play a role. This finding suggests that meticulous attention to detail regarding the technical aspects of laryngological procedures and the size and position of the endotracheal tube and thorough and conscientious follow-up are essential in the airway management of infants with PDs with or without CFMs.

Dilation or hyperplasia of submucosal glands was observed in 5 of 10 specimens in the study group and 3 of 7 in the control group. All but 1 of these individuals had a history of airway intervention. In each group, several individuals with a history of airway manipulation had no evidence of such findings. One researcher noted a topographic relationship be-

tween glandular and lymphatic tissues and suggested a possible role in the production of secretory immunoglobulins.¹¹ The relationship between dilation or hyperplasia of submucosal glands and an immunologic response to bacterial and viral pathogens is, currently, theoretical. In this study, no relationship was found between anomalous submucosal glands and airway manipulation, sex, or age.

CONCLUSIONS

In general, the primary laryngeal histologic findings of specimens from individuals with PDs with or without CFMs do not differ significantly from those of specimens from normal individuals. However, individuals with PDs with or without CFMs appear to be more susceptible to acquired laryngeal injury. All patients with PDs require meticulous airway management.

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HUMAN PAPILLOMAVIRUS AND RISK OF LARYNGEAL CANCER

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We determined the relationship between human papillomavirus (HPV) infection and the HPV types detected in 44 patients with squamous cell carcinoma, 10 laryngeal leukoplakia patients, and 12 patients evaluated for benign laryngeal conditions (controls). The sources of HPV DNA were from brushings from the upper respiratory tract and lesion (benign or malignant), oral rinses, and biopsies of patient lesions. Polymerase chain reaction (PCR) and DNA sequencing were used to identify and type HPV. We detected HPV in 25.0% (11/44) of patients with laryngeal cancer, in 30.0% (3/10) of patients with laryngeal leukoplakia, and in 16.7% (2/12) of noncancer controls. Patients with cancer were not more likely to be identified with oncogenic HPV types (18.2%) than either the leukoplakia group (20%) or the control group (16.7%). An increased risk of disease was associated with current tobacco use and former alcohol drinking in cancer patients versus controls and in leukoplakia patients versus controls (all $p < .05$). After we controlled for tobacco and alcohol effects on the risk of disease, exposure to oncogenic HPV types was associated with an increased risk of laryngeal cancer (odds ratio = 3.0) and of laryngeal leukoplakia (odds ratio = 6.0) compared to controls, although the results were not statistically significant. This study suggests that although HPV infection and HPV oncogenic types are not found at a higher frequency in laryngeal cancer or laryngeal leukoplakia as compared to controls, infection is associated with an increased risk of disease after controlling for the effects of alcohol and tobacco use.

KEY WORDS — case control study, human papillomavirus, laryngeal cancer.

Human papillomavirus (HPV) causes virtually all cancers of the uterine cervix and a large portion of other genital tumors in both men and women.¹ In contrast, studies of HPV infection in laryngeal or pharyngeal squamous cell carcinomas (SCCs) have reported a wide variation in frequency, ranging from 22% to 83%, and exhibiting a spectrum of oncogenic and nononcogenic HPV types.²⁻⁹ Other possible risks and confounders such as age, gender, and tobacco and alcohol use usually have not been evaluated in studies of HPV risk associated with laryngeal cancer. Nor has the sexual behavior of this sexually transmitted disease been studied in participants, which may be a mechanism by which HPV is introduced into the oral cavity and larynx. Detection of HPV in the larynx of nondiseased patients also has varied, from 7% to 64%.^{10,11} Morgan et al² found 70% of laryngeal malignancies to contain HPV, with 50% having high-risk (HR), oncogenic types. All patients were smokers, and half had undergone radiotherapy before HPV assessment, which effect on infection is unknown. Pérez-Ayala et al³ evaluated 48 patients with laryngeal carcinomas and identified HPV-16 in 54%, but reported no information on smoking or alcohol

habits. Clayman et al⁴ exhibited detectable HPV in 46% (30/65) of laryngeal and hypopharyngeal cancer specimens and found that HPV of unspecified types was associated with a 2.4-fold increased risk of recurrence. In contrast, Fouret et al¹² identified HPV in only 5.1% of laryngeal and 12.0% of hypopharyngeal squamous cell carcinoma specimens from 126 patients. However, the HPVs identified were primarily oncogenic types: HPV-16/18 and HPV-31/33. They also found that the frequency of HPV infection was significantly greater in nonsmokers than in smokers (50.0% versus 8.5%).¹³ In a separate study of precancerous laryngeal lesions, they showed a low HPV frequency, 10.5%.¹⁴ Using restriction fragment length polymorphism to type amplified HPV DNA in laryngeal cancers, Suzuki et al¹⁵ found 22.0% with HPV-16 and 4.9% with HPV-18, whereas HPV types 6, 11, 31, 33, 42, 52, and 58 specifically were not detected. Other studies¹⁶⁻¹⁸ also have found HPV in only a small percentage of laryngeal carcinoma patients (8% to 9.4%), most of whom were smokers. Among those who examined noncancerous lesions of the larynx, Rihkanen et al¹⁰ examined biopsies from patients with voice disorders (nodules, polyps, chron-

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ic laryngitis), finding HPV in 19%. The rate of HPV detection was unrelated to age, gender, tobacco use, or type of voice problem. A small autopsy study of normal larynges showed a 25% positivity rate (3/12) for HPV-11, but not HPV-16 or -18; all of the larynges were taken from current smokers at the time of death.¹¹

The purpose of this study was to evaluate the frequency and types of HPV in individuals with laryngeal carcinoma, laryngeal leukoplakia, and laryngeal noncancerous lesions and voice problems (controls). Another objective was to evaluate the association between HPV infection and risk of developing disease independent of previously identified risk factors for laryngeal malignancy and leukoplakia: alcohol and tobacco. In addition, the potential for using an oral rinse to screen for HPV DNA as a marker to predict an increased risk of premalignant and malignant lesions was examined, in a comparison of oral rinses, laryngeal brushings, and tumor biopsies in these patient groups.

METHODS

Between November 1994 and August 1996, a random sample of patients with diagnoses of laryngeal cancer made at the University of Iowa Health Care, College of Medicine, Department of Otolaryngology, and the adjacent Veterans Affairs Medical Center were approached for participation in the study. The enrolled patients had new diagnoses with pathological confirmation of laryngeal or hypopharyngeal cancer (ICD-0: C13.0-13.9, C32.0-32.9; hypopharynx, glottis, supraglottis, subglottis, and larynx not otherwise specified). All the cancers were squamous cell carcinomas (SCCs). The tumors were staged with the TNM system. In this study, "lower stage" refers to all categories of TNM I and II and "higher stage" refers to TNM III and IV. Laryngeal leukoplakia patients and noncancer controls were solicited from the otolaryngology clinic for comparison. The leukoplakia cases were identified clinically, but there was no histopathologic evaluation. The lesions included red or white areas of epithelial thickening not suggestive of malignancy. Only patients who were undergoing endoscopy and general anesthesia for assessment of benign laryngeal lesions or conditions were included as controls, because laryngeal cell brushings collected for HPV DNA assessment needed to be similar to the procedures used to assess HPV in the cancer and leukoplakia cases. As a result of their diagnosis of benign laryngeal conditions, the controls were more likely to be younger and more likely to be female than the patients in the case groups. Most of the control patients were being seen for a voice problem such as nodules, polyps, or inflammatory condi-

tions of the larynx. Fewer than 5% of study patients or controls refused or were unable to complete the questionnaire because of illness associated with their condition.

Risk Factor Questionnaire. After informed consent was obtained, the patients were given a questionnaire to complete that included information about alcohol and tobacco use, sexual behavior, and sexually transmitted diseases in the patient or in any of his or her partners. Age, gender, income, education, and occupation and related chemical exposures were included to evaluate their association with disease.

Cytologic Specimens. This study examined exfoliated cells collected from an oral rinse and from brushings of cells taken from the larynx for detection of HPV DNA. The oral rinse consisted of 10 mL of normal saline solution swished and gargled for 30 seconds. Patients who wore dentures were instructed to remove these before the specimen collection. The rinse was expectorated into a medicine cup used to transfer the specimen into a 12-mL tube. Additional specimens were collected by a sterile 1.7-mm cytobrush that was passed through the endoscopy tube while the patient was under anesthesia for a panendoscopy or undergoing surgery for biopsy and dissection. The physician brushed the larynx, including normal-appearing epithelium and the site of the tumor or benign lesion. The cytobrush was then cut and placed into a 12-mL tube of normal saline solution. The tube was vortexed to loosen cells, and the brush was discarded before freezing the sample. Oral rinses were collected from all 12 controls, 9 leukoplakia cases, and 37 cancer cases. Laryngeal brushings were available from all controls, 9 leukoplakia cases, and 39 cancer cases.

Because it was uncertain whether the collection procedure would provide an adequate number of nucleated squamous cells for polymerase chain reaction (PCR) amplification of HPV, cells were counted. The number of exfoliated nucleated squamous cells collected from the rinses was estimated by counting with a hemacytometer. An oral rinse yielded an average of 1.2 million cells from controls and 1.7 million cells from leukoplakia and laryngeal cancer patients. The DNA from each oral rinse sample was resuspended in TE buffer (10-mmol/L Tris hydrochloride, 1-mmol/L ethylenediaminetetraacetic acid, pH 8.0) so that each PCR had input DNA from the same number of cells. The number of cells obtained from the brushings was estimated after Cytospin concentration of a 200- μ L aliquot. Brushings yielded an average total of 16,000 cells from the controls, 12,000 cells from the leukoplakia cases, and 17,000 cells from the laryngeal cancer cases. Extracted DNA from

10% of each brushing sample was used for PCR amplification.

Biopsies. Biopsy material also was collected to detect HPV DNA. Tissue was not available from all participants, because most of the tissue was consumed for histologic diagnosis. None of the noncancer controls had biopsies, whereas 2 of the leukoplakia cases and 23 of the cancer cases had adequate tissue for HPV testing after pathology assessment. The biopsy specimens were immersed in liquid nitrogen as quickly as possible after removal from the patient and then stored at -70°C . The amount of biopsy material processed for DNA extraction ranged from 1 to 63 mg. The biopsy specimen was ground to a powder with a mortar and pestle under liquid nitrogen. The DNA was then extracted from the sample with the Qiagen RNA/DNA System Kit (Qiagen) and resuspended in 100- μL TE. Four microliters of the DNA solution was used in each PCR amplification. The PCR amplification parameters were identical to those used for the oral rinse and laryngeal brushing samples. The size of the portion of the biopsy used for DNA extraction did not correlate with success of amplification of β -globin or with HPV detection. Because we were unable to PCR-amplify β -globin or HPV DNA from the frozen biopsy material of 2 laryngeal cancer patients, DNA was extracted from formalin-fixed, paraffin-embedded blocks of the tumors by means of the QIAamp DNA Blood Kit (Qiagen). The dimensions of the tumor in the sections were $40\text{ }\mu\text{m} \times 2\text{ mm}^2$ and $40\text{ }\mu\text{m} \times 14\text{ mm}^2$. The PCR amplification used 1.3% of the extracted DNA as a template.

HPV DNA Detection. Oral rinse and laryngeal brushing cells were first digested with proteinase-K in TE buffer. Then the DNA was extracted with phenol-chloroform-iso-amyl alcohol solution, precipitated with 2 volumes of 100% ethyl alcohol, and dissolved in TE buffer to the equivalent of 7,500 cells per microliter. The HPV DNA was PCR-amplified with MY09/MY11 HPV L1 primers,¹⁹ with DNA from approximately 30,000 cells used as a template. An additional 3' primer that facilitates HPV-51 amplification was included.²⁰ Primers to amplify a 294 bp portion of the β -globin gene were used as an internal control.²¹ Each 50- μL reaction contained PCR buffer with 1.5-mmol/L magnesium chloride (Boehringer-Mannheim), 200- $\mu\text{mol/L}$ each deoxyribonucleotide (deoxyadenosine triphosphate [dATP], deoxyguanosine triphosphate, deoxythymidine triphosphate, and deoxycytidine triphosphate), 2 U Taq DNA polymerase (Boehringer-Mannheim), 56-pmol/L TaqStart antibody (Clontech), 37.5 pmol each MY09 and MY11 primers, 12.5 pmol each globin primer, 5 pmol HPV 51 primer, DNA from approximately 30,000 cells (100 ng), sterile water, and a 50- μL over-

lay of mineral oil. The PCR amplification was performed in a thermocycler (Perkin-Elmer Cetus) as follows: 94°C for a 3-minute denaturation (93°C for 30 seconds, 55°C for 30 seconds, 72°C for 1 minute) for 35 cycles of amplification, and 72°C for a 10-minute extension. Each set of PCR amplifications included positive and negative controls. Amplification of HPV DNA was tentatively judged positive if electrophoresis on a 1% agarose gel showed an approximately 450 bp band by staining with ethidium bromide or if a signal was detected by nylon membrane "dot blot" hybridization with [α - ^{32}P]dATP-labeled generic HPV probes.²²

HPV Typing. Automated DNA sequence analysis was used to confirm and type the HPV DNA. Amplified DNAs were purified with the Wizard PCR Preps DNA Purification Kit (Promega, Madison, Wis) and sequenced on a PE Applied Biosystems automated sequencer (Perkin Elmer Cetus, Foster City, Calif). When insufficient DNA was present for sequencing, HPV DNA sequences were reamplified for 25 cycles in a second PCR reaction with 1 μL of the original PCR product and the MY09/MY11 primers or with MY09/GP5+²³ used as heminested primers. The DNA sequences were compared with those of HPV known isolates on the GenBank database by the BLAST sequence analysis program.²⁴ A sample was identified as a specific HPV type if it matched a type on the database by more than 90%. Several of the mucosal oncogenic, high-risk HPV (HPV-HR) types, those most commonly associated with an increased risk of cervical dysplasia and carcinoma and those most closely related to them, were found in this study: HPV-16, -18, -31, -45, and -70. Sequencing also identified mucosal nononcogenic and cutaneous HPVs: HPV-11, -61, and sequences matching GenBank Accession numbers U12480, AF042005, and L38388. The mucosal nononcogenic and cutaneous HPV types are considered low-risk (HPV-LR), because of their usual association with benign lesions, or because their DNA sequence is closer to that of benign types than to that of the high-risk types.

Statistical Analyses. The analyses focused on detecting differences in the 3 patient groups (cancer cases, leukoplakia cases, and controls) with regard to potential risk factors. All statistical tests compared the control group to each of the case groups. The Wilcoxon rank sum test was used to test for group differences for continuous variables (ie, age, education, number of sex partners, and tobacco and alcohol dose-duration variables). Pearson's χ^2 and Fisher's exact tests were used to test for group differences for alcohol and tobacco categories, respectively, at $p < .05$. Multivariate logistic regression was used to compare the risk of laryngeal cancer or leu-

TABLE 1. MEDICAL HISTORY AND DEMOGRAPHIC CHARACTERISTICS OF CASES AND CONTROLS

	<i>Cancer</i>		<i>Leukoplakia</i>		<i>Control</i>	
	%	No.	%	No.	%	No.
Medical history						
Polyps	2.3	1	20.0	2	16.7	2
Nodules	2.3	1	10.0	1	0.0	0
Vocal cord cyst	0.0	0	0.0	0	25.0	3
Polypoid corditis	0.0	0	10.0	1	0.0	0
Papilloma	2.3	1	0.0	0	0.0	0
Demographics						
Age (average)		62		56		49
Education (average)		12.0		13.0		13.6
Gender: male	65.9	29	70.0	7	41.8	5
Race: white	97.3	43	100.0	10	91.8	11

koplakia to controls in association with HPV infection, controlling for other potential risks and confounders (ie, alcohol, tobacco, age). Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated by a 2-tailed test of significance, and all tests were reported at $p < .05$.

RESULTS

The study included 44 patients with laryngeal squamous cell carcinoma, 10 patients with laryngeal leukoplakia, and 12 control subjects with benign laryngeal lesions who had never had a previous diagnosis of head and neck cancer. Eighty-two percent of the cancer patients in this study had a diagnosis of a first primary, 16% had a recurrence of a first primary, and

2% had a second primary. The prior laryngeal disease history noted the following in 1 or more of the patient groups: polyps, vocal cord cyst, nodules, polypoid corditis, and papilloma (Table 1). Cancer and leukoplakia patients were older than controls (Table 1), were more likely to be male, and had less education than controls. All groups were primarily non-Hispanic white.

Table 2 shows the frequency of tobacco and alcohol use in the 3 groups. Those with laryngeal cancer and leukoplakia were more likely to have ever drunk alcoholic beverages and to be ex-drinkers than the noncancer controls (Table 2). There was no significant difference between case and control groups and current drinking status. There were no significant dif-

TABLE 2. RISK FACTORS AMONG CASES AND CONTROLS

	<i>Cancer</i>		<i>Leukoplakia</i>		<i>Control</i>	
	%	No.	%	No.	%	No.
Alcohol						
Never user	20.5	9	10.0	1	41.7	5
Ex-user	40.9*	18	60.0*	6	8.3	1
Current user	38.6	17	30.0	3	50.0	6
Average drinks per week	27*		23.2*		10	
Tobacco						
Never user	2.3	1	0.0	0	30.8	3
Ex-user	50.0*	22	20.0*	2	38.5	5
Current user	47.7*	21	80.0*	8	30.8	4
Average pack-years	59.3†		51.7§		22.2	
No. of sex partners						
1-2	36.4	16	30.0	3	54.6	6
3-4	13.7	6	10.0	1	9.1	1
≥5	50.0	22	60.0	6	36.4	4
Median	4.5		6.5		2.0	
Age at first oral-genital sex	23.3		24.6		21.1	
No. of years oral-genital sex	18.4		20.2		19.4	

Significance values compare case group to control group.

* $p < .05$.

† $p < .01$.

§ $p < .07$.

TABLE 3. HPV PREVALENCE AMONG CASES AND CONTROLS

HPV Status	Cancer (HPV+, 11/44)					Leukoplakia (HPV+, 3/10)					Control (HPV+, 2/12)			
	%	No.	No.			%	No.	No.			%	No.	No.	
			O (n = 37)	L (n = 39)	B (n = 23)			O (n = 9)	L (n = 9)	B (n = 2)			O (n = 12)	L (n = 12)
HPV+	25.0 ¹	11 ²	9	5 ³	2 ³	30.0 ¹	3	1	2	0	16.7 ¹	2	2 ⁴	1 ⁴
HPV-LR	9.1 ¹	4	4	0	0	10.0 ¹	1	1	0	0	8.3 ¹	1	0	1
HPV-HR	18.2 ¹	8 ⁵	5 ³	5 ³	2 ⁴	20.0 ¹	2	0	2	0	16.7 ¹	2	2	0
Types														
11	2.3	1	1	0	0	0.0	0	0	0	0	0.0	0	0	0
16	13.6	6	4 ^{2,3}	4 ³	1 ⁴	10.0	1	0	1	0	8.3	1	1	0
18	0.0	0	0	0	0	0.0	0	0	0	0	8.3	1 ^{2,4}	1 ⁴	0
31	2.3	1	0	1 ²	1	0.0	0	0	0	0	0.0	0	0	0
45	2.3	1	1 ⁴	0	0	0.0	0	0	0	0	0.0	0	0	0
61	0.0	0	0	0	0	0.0	0	0	0	0	8.3	0	0	1 ²
70	0.0	0	0	0	0	10.0	1	0	1	0	0.0	0	0	0
AF042005	4.5	2	2	0	0	0.0	0	0	0	0	0.0	0	0	0
L38388	2.3	1	1	0	0	0.0	0	0	0	0	0.0	0	0	0
U12480	0.0	0	0	0	0	10.0	1	1	0	0	0.0	0	0	0

HPV — human papillomavirus, O — oral source of HPV DNA, L — laryngeal source of HPV DNA, B — biopsy source of HPV DNA, LR — low-risk–nononcogenic types, HR — high-risk–oncogenic types.

¹Based on number of individuals.

²Individual had multiple types.

³Three patients were HPV+ from more than 1 source.

⁴Two patients were HPV+ from more than 1 source.

⁵Four patients were HPV+ from more than 1 source.

ferences in average duration of alcoholic intake or type of alcohol product between case and control groups. However, the average dose-duration in drinks per week was significantly higher in the two case groups compared to the control group.

Those with cancer or leukoplakia were significantly more likely than controls to have ever used tobacco products (ie, combined use of cigarette, cigar, pipe, chewing tobacco, and snuff) and to do so currently. Table 2 shows that compared to never users, the risk of disease among ex-users ($p < .05$) or current users ($p < .05$) was significantly increased in cancer cases compared to controls and in current users with leukoplakia compared to controls ($p < .05$). The risk associated with tobacco dose-duration by pack-years also was elevated among cancer (59.3 pack-years, $p = .001$) and leukoplakia cases (51.7 pack-years, $p = .069$) compared to controls (22.2 pack-years). There were no significant differences in the average age at which the case or control groups started or quit smoking cigarettes (data not shown). However, when examined by usage of cigarettes, the most common tobacco product used, the patients in the case groups smoked more cigarettes per day on average than the controls (Table 2). Few individuals regularly used cigars, pipe, chewing tobacco, or snuff.

Cancer and leukoplakia patients had a higher me-

dian number of sexual partners during their life compared with controls, but the differences were not statistically significant (Table 2). The control group was significantly more likely to report having oral-genital sex than were the cancer patients ($p < .05$), but not the leukoplakia patients (cancer, 27%; leukoplakia, 50%; controls, 67%). There were no significant differences in initial age or duration of oral-genital sex. No one reported ever having oral-anal sex. Only leukoplakia patients ever reported having HPV-related genital warts. The cancer and leukoplakia patients were more likely to report oral herpes (50%, 40% versus 25%), but no group reported a history of genital herpes.

Table 3 shows the frequency and types of HPV detected overall (HPV+), low-risk–nononcogenic types (HPV-LR), and high-risk–oncogenic types (HPV-HR) in the cancer, leukoplakia, and control groups. Because increased risk of cervical and oral cancers has been associated with oncogenic types, these are the focus of interest in this analysis. Nonetheless, nononcogenic HPV types by case-control group also were examined for differences in frequency. The sites of infection were based on collections from oral or pharyngeal cavity cells, laryngeal cells, and biopsy tissue material from identified lesions. The 2 case groups showed similar HPV+ prevalence: 25.0% (11/44) in cancer, 30.1% (3/10) in leukoplakia,

TABLE 4. FREQUENCY OF HPV-HR, TNM STAGES, AND TOBACCO AND ALCOHOL USE BY CANCER SITE

Site	No.	HPV-HR	Stage					Tobacco			Alcohol		
			0	I	II	III	IV	C	E	N	C	E	N
Hypopharynx	5	0	0	0	0	1	4	3	2	0	3	2	0
Supraglottic	19	1	0	2	0	6	11	12	7	0	8	8	3
Glottic	20	7	1	14	1	2	2	6	13	1	6	8	6

C — current user, E — ex-user, N — never user.

and only 16.7% (2/12) in controls. However, cancer cases were no more likely to show oncogenic HPV types than leukoplakia cases or controls (18.2%, 20.0%, and 16.7%, respectively). Nor was there a difference in the frequency of HPV-LR, nononcogenic, types across groups. The most frequent oncogenic HPV type identified was HPV-16: 75% in cancer, 67% in leukoplakia, and 50% in controls. Other HPV oncogenic types identified were HPV-18, -31, -45, and -70 — again, more frequently in the malignant cases, with the exception of HPV-18, which was found as a multiple infection in an oral rinse from a control.

Overall, HPV was most likely to be detected in oral rinses, followed by laryngeal brushings, and then biopsy material. When examined by these 3 specimen collection sites, cancer cases were about as likely to show HPV-HR types from rinses of the oral cavity as from direct brushings of the larynx. Cancer cases had a greater detection of low-risk types only in the oral cavity rinses. The 2 case groups from whom biopsy material was available showed that HPV was detected only in cancer cases, and only with high-risk types. Four cancer cases had multiple sources from which HPV of the same type was detected: 3 with HPV-16, 1 with HPV-31. Five cancer cases had HPV only in the oral rinse, 2 only in the laryngeal brushings, and none only in the biopsy material. One cancer case had HPV-45 in the oral rinse and HPV-16 in the biopsy (both are HPV-HR types). Two HPV-HR types were detected in the larynx of leukoplakia cases only, and none in either the oral rinse or biopsy. One control was HPV+ from multiple sources (oral cavity and larynx), but with different HPV types: HPV-61 in the larynx, and HR HPV-18 in the oral cavity.

The risk of laryngeal cancer and leukoplakia associated with HPV-HR infection was evaluated in comparison to controls, by multivariate logistic regression. Predictors of disease status included HPV-HR (compared to those who were HPV-negative), tobacco dose-duration (number of packs or equivalent per day multiplied by the number of years used), alcohol dose-duration (number of drinks per day multiplied by the number of years of drinking), and age. Those with HPV-LR infection only were excluded

from the analyses. The findings suggested that although all of these factors were associated with an increased risk of disease, because the sample size was small, the results were unstable. None of these risks reached statistical significance. Nonetheless, the analyses revealed that the risk associated with HPV-HR types compared to HPV-negative subjects was increased in both cancer (OR = 3.0) and leukoplakia (OR = 6.0), with the effects of alcohol, tobacco, and age controlled for.

Among the cancer cases, there was a similar frequency of tumors that developed in the supraglottic and glottic areas (44% each), with the remaining 12% in the hypopharynx (Table 4). The laryngeal leukoplakias were located in the glottis (78%) and supraglottis (22%; data not shown). Whereas most of those with cancer in the hypopharynx and supraglottis were in TNM stages III and IV, glottic tumors were most often diagnosed in early stage I. None of the tumors in the hypopharynx was detected with HPV-HR, whereas oncogenic types seemed to be found preferentially in the glottis of laryngeal cancer patients and diagnosed at an early stage, with 6 HPV-16 (5 stage I, 1 stage IV) and 1 HPV-45 (stage 0). Among those with HPV-16, there were 4 ex-tobacco users—never drinkers in stage I, another was a current tobacco user—never drinker in stage I, and 1 was a never tobacco user—alcohol user who was identified in stage IV. The patient with HPV-45 was an ex-tobacco user—never drinker. Only 1 HPV-HR infection (HPV-31) occurred in a supraglottic tumor, stage IV, to an ex-tobacco user—ex-drinker.

DISCUSSION

Compared to controls, patients with SCC of the larynx in this study had a higher frequency of HPV infection. Although there was not a significant difference in the frequency of HPV-HR detected in laryngeal cancer cases and controls (18.2% versus 16.7%), the sample size of the control group ($n = 12$) was very small, and a single change in a patient HPV test result would cause a major shift in the HPV frequency. As supporting evidence that HPV-HR is lower in rinses from controls, we have recently completed a case control study of oral cancer risk associated with HPV. That study included a large group of noncancerous adult controls ($n = 333$) for whom

oral rinses were evaluated for HPV DNA, by means of the same laboratory methods described in this study. These age- and gender-matched controls also are closer in age to the laryngeal cancer group in this study, with an average of 60. The findings in the oral cancer-HPV risk study indicated that only 11% of controls had HPV-HR types in oral rinses, compared with 22.8% of the oral cancer cases; this finding suggests that a true difference in HPV frequency exists between those with and those without cancer. Further, the frequency of HPV-HR among the oral cancer and laryngeal cancer cases is similar.

This is one of the few studies to sample squamous cells from both the oral cavity and from the site of the lesion for detection of HPV DNA in laryngeal cancer cases and in controls with benign laryngeal lesions. Some studies have attempted to evaluate HPV status in presumably normal tissue in laryngeal cancer patients. In this study of laryngeal cancer cases, detection of HPV was more likely to occur in oral cavity rinses than in the tumor. Productive HPV infection occurs only in differentiating squamous epithelium. When HPV has been detected in tumors, the DNA is present as integrated or as low numbers of episomes. This may reflect the restriction of productive HPV infection, leading to a high viral copy number in benign or mildly dysplastic tissue but not to malignant cells. This study based HPV outcome on evaluating cells from similar (laryngeal) sites in controls who are free of cancer, dysplasia, or leukoplakia or any known HPV-related lesion.

Our data confirm a previous observation that glottic SCCs show a higher HPV-HR positivity than do supraglottic SCCs,⁹ and that the hypopharynx shows the lowest positivity rate. Further, HPV was more likely to be detected in lower-stage disease (TNM I or II). Although others also have seen this relationship,⁹ it is unclear whether it is due to easier detection of HPV DNA in lower-stage tumors compared to higher stages (TNM III or IV). Alternatively, this finding may indicate that HPV-HR laryngeal malignancies tend to be less aggressive.

This also is the first study to type HPV in laryngeal lesions by DNA sequencing. The procedure allows for identification of additional types not detected by probes designed specifically to identify HPV types found in cervical cancer. However, these types may be different from those that infect the respiratory tract. Sequencing confirmed the predominance of the oncogenic HPV-16 type in malignant tumors of the larynx, as also has been found in the majority of cervical and oral carcinomas.

Our data suggest that although the prevalence of

HPV-HR in laryngeal cancers is significantly lower than that in the cervix, it is similar to that detected in our and other studies of HPV-HR among oral and laryngeal cancer and noncancer control patients.^{16,18,22} This study is the first to evaluate the independent association between HPV oncogenic types and both leukoplakia and malignant laryngeal cancer, and to control for the effects of lifetime tobacco and alcohol use. Unlike the findings in our oral cancer study, and possibly because of the small sample size in this study, the risks were increased but not statistically significant.

One other study has compared biopsy to brush material of the tumor and margin for HPV detection in malignant biopsies of the larynx. The result showed a positivity rate of 66.7% from biopsy material, compared to 16.7% in brushings from the tumors.²⁵ A comparison group of benign laryngeal lesions also had a low rate: 14.3% in biopsy material. (No brushing was performed on this group.) The patients with benign and malignant lesions were all current smokers and positive for HPV-6 or -16, but not HPV-11, -18, or -31. No other HPV-HR types were assessed. The authors concluded that a brush technique was inadequate for detecting HPV DNA, although the sample size was small ($n = 7$). According to our studies, however, it is likely that some of these results may be explained by inconsistent amplification of specimens, with wide variation in the number of cells collected in the larynx of different patients. In our study, all brush specimens were assessed for nucleated squamous cells by Cytospin concentration. The PCR amplification of β -globin of all of our brushing samples confirmed the presence of adequate cellular DNA. Thus, we would conclude that this procedure is an adequate technique for clinical use when standardization and sensitivity testing are observed.

A large, multicenter case control study of HPV associated with the risk of laryngeal cancer, using the techniques that this laboratory has established for identifying HPV in head and neck specimens, would provide a more reliable foundation for our initial findings, suggesting by multivariate analyses that HPV-HR types are associated with an increased risk of laryngeal cancer and leukoplakia. Alternatively, such a study would provide a more substantial basis for refuting the findings in this and the other small investigations available to date. Assessment of biopsy material for gene expression and integration would provide strong evidence that HPV is causative in the development of laryngeal carcinoma. An epidemiological project could further evaluate whether certain sites in the larynx are more prone to become infected with HPV DNA, whether HPV can be identified more readily in early stages of disease, and whether one

source of HPV DNA — oral, laryngeal, or tumor — is a better predictor of subsequent disease development or progression than another. It also would pro-

vide a much-needed assessment of the overall prevalence of HPV in the larynx of adult nondiseased (control) patients.

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LARYNGEAL STENOSIS AFTER SUPRACRICOID PARTIAL LARYNGECTOMY

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The purpose of this study was to review the incidence, risks, management, and outcomes of nontumoral laryngeal stenosis after supracricoid partial laryngectomy (SCPL) in a case series of 376 consecutive SCPLs performed at 1 institution from 1975 to 1995 with a minimum of 3 years of follow-up. Post-SCPL nontumoral symptomatic laryngeal stenosis was defined as an inability to decannulate patients before the 60th postoperative day (group 1) or the development of dyspnea (in patients without local recurrence) after an initial period of prolonged, successful decannulation (group 2). Of 376 SCPLs performed, nontumoral symptomatic laryngeal stenosis developed in 14 (3.7%). There were 7 patients (1.85%) in group 1 and 7 patients (1.85%) in group 2. In univariate analysis, none of the following variables appeared to be statistically related to the risk of immediate stenosis (group 1): age, gender, comorbidity, diabetes mellitus, symptomatic gastroesophageal reflux, arteritis, preoperative radiotherapy, arytenoid cartilage disarticulation, type of reconstruction performed, and postoperative radiotherapy. A delayed laryngeal stenosis (group 2) was statistically more likely to occur if the reconstruction performed at the time of SCPL was a cricohyoidopexy ($p = .01$). Successful management of the laryngeal stenosis without permanent tracheostomy was achieved in 5 group 1 patients and 3 group 2 patients. We believe that stenosis in group 1 patients arose through technical error, whereas group 2 patients seemed to suffer from problems of healing, mainly cicatricial narrowing of the airway at the site of the cricohyoid impaction, or pexis. As a result, whereas laryngeal stenosis in group 1 patients was usually more easily correctable through dilation, laser incision, or resection of redundant tissue or revision of the impaction, laryngeal stenosis in group 2 patients presented a more difficult and frustrating complication. The management and outcomes of these patients are presented.

KEY WORDS — complications, laryngeal stenosis, supracricoid partial laryngectomy.

INTRODUCTION

The current literature supports the fact that supracricoid partial laryngectomy (SCPL) with cricohyoidopexy (CHP), cricohyoidoepiglottopexy (CHEP), or tracheohyoidoepiglottopexy (TCHEP) is a viable option for the management of selected endolaryngeal carcinomas.¹⁻²³ Although much of the literature has been devoted to the oncological analysis and functional evaluation of SCPL,¹⁻²³ little has been specifically written about the major complications of this procedure.²⁴⁻²⁶ These include pneumonia from aspiration, rupture of the pexis, laryngocele, and laryngeal stenosis or compromised airway. This retrospective review of 376 consecutive patients who underwent SCPL for select endolaryngeal carcinoma at a single institution was undertaken to document the incidence, natural history, management, and outcome of nontumoral symptomatic laryngeal stenosis.

MATERIALS AND METHODS

Between 1975 and 1995, 376 SCPLs were performed in the Department of Otorhinolaryngology—

Head and Neck Surgery at Laënnec Hospital of the University of Paris V in Paris, France. There were 350 men (93%) and 26 women (7%) with a mean age of 57 years (range, 23 to 85 years). Table 1 provides the TNM staging according to the 1997 American Joint Committee on Cancer classification system at the time of the original diagnosis for 346 patients with a previously untreated endolaryngeal carcinoma.²⁷ Twenty-seven patients underwent salvage SCPL after vertical partial laryngectomy ($n = 13$) or radiotherapy ($n = 14$), and 3 additional patients underwent SCPL for reasons other than carcinoma. Two patients underwent SCPL for correction of a laryngeal steno-

TABLE 1. TNM STAGING OF 346 PATIENTS WITH PREVIOUSLY UNTREATED INVASIVE ENDOLARYNGEAL CARCINOMA

	N0	N1	N2	N3
T1	45			
T2	169	11	5	1
T3	81	15	5	2
T4	8	3	1	

All patients were clinically M0.

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TABLE 2. ALCOHOL INTAKE, TOBACCO INTAKE, AND COMORBIDITY INDEX WEIGHTED SCORE AMONG 376 PATIENTS

	No.	%
Tobacco intake (pack-years)		
0	18	4.8
1-20	57	15.1
21-40	166	44.1
41-60	72	19.2
>60	43	11.4
Alcohol intake (g/d)		
0	55	14.6
<40	128	34.1
41-80	125	33.2
>80	68	18.1
Comorbidity index weighted score*		
0	198	52.5
1	109	28.9
2	48	12.8
3	13	3.4
4	6	1.6
5	1	0.2
7	1	0.2

*According to comorbidity weighted index of Charlson et al.²⁸

sis, and 1 patient underwent SCPL for extensive laryngeal papillomatosis. Table 2 presents the tobacco consumption, alcohol intake, and comorbidity data according to the comorbidity index weighted score of Charlson et al.²⁸

The primary tumor required partial resection of 1 arytenoid cartilage in 85 patients (22.6%) and total resection of 1 arytenoid cartilage in 109 patients (29%). In the remaining 182 patients (48.4%), both cricoarytenoid units were left completely intact. The reconstruction performed, dictated by the extent and location of the primary tumor, was a CHEP²¹ in 217 patients (57.7%), a CHP²³ in 137 patients (36.4%), and a TCHEP²² in 22 patients (5.9%). Seventeen surgeons managed the patients; all used the same guidelines and techniques.^{18,19,21-23} Fourteen patients underwent preoperative radiotherapy to the larynx (mean dosage delivered, 60 Gy; range, 40 to 75 Gy). Fifty-four patients underwent postoperative radiotherapy (mean dosage delivered, 50 Gy; range, 26 to 67 Gy).

For the purposes of this study, we defined post-SCPL stenosis as either an inability to decannulate the patient by the 60th postoperative day (group 1) or development of dyspnea beyond this period after an initial, prolonged period of successful decannulation (group 2). All patients in whom dyspnea developed after the immediate postoperative period were systematically evaluated for the possibility of loco-

regional recurrence. Evaluation included clinical evaluation with indirect laryngoscopy, laryngeal computed tomographic scanning, and endoscopy. When indicated, biopsy was performed on suspicious areas at the time of endoscopy. Twenty-five patients (6.7%) whose airway impairment was subsequently proven to be a result of local recurrence were excluded from this review.

Follow-up data were collected at the time of regular visits to our department. The minimum follow-up for these patients was 42 months, except for 7 patients (1.8%) who were lost to follow-up before their third postoperative year. Univariate analysis was carried out in group 1 and group 2 patients for a potential statistical relationship between the development of a nontumoral symptomatic laryngeal stenosis and the following variables: age, gender, comorbidity, diabetes mellitus, symptomatic gastroesophageal reflux, arteritis, preoperative radiotherapy, arytenoid cartilage disarticulation, type of reconstruction performed, and postoperative radiotherapy. The nonparametric Mann-Whitney U test and the Fisher exact test were used for quantitative and qualitative variable analysis, respectively. Statistical significance was set at the .05 level.

RESULTS

Of 376 consecutive SCPLs, 14 patients (3.7%) met the aforementioned criteria for nontumoral, symptomatic post-SCPL laryngotracheal stenosis. Of these, 9 were male and 3 were female. Stenosis after SCPL, as defined by an inability to decannulate the patient by the 60th postoperative day, occurred in 7 patients (group 1). Stenosis developed in 7 other patients at some time interval (3 months to 13 years) after successful decannulation (group 2).

Among the group 1 patients, the causes of stenoses included synechiae between the vocal processes of the spared arytenoid cartilages in 1 patient, posterior prolapse of the epiglottis in 3 patients, rupture of the pexis in 1 patient, and excessive granulation tissue at the impaction line in 2 patients. In univariate analysis, no significant statistical relationship could be demonstrated between the development of group 1 stenosis and the variables under analysis. The management of patients in group 1 relied on the CO₂ laser in 6 patients (to transect synechiae, to resect granulation tissue, to incise redundant tissue, or to resect a prolapsed epiglottis) and revision of the impaction in 1 patient who had a ruptured impaction. One of the 5 group 1 patients required multiple laser treatments over a 3-year period, and ultimately all attempts at decannulation failed in this patient. Five other group 1 patients were successfully decannulated

without recurrence of the dyspnea, and the final group 1 patient ultimately required total laryngectomy.

All group 2 patients had cicatricial narrowing of the airway at the level of the cricohyoid impaction. In addition, 1 patient also had ankylosis of the spared cricoarytenoid joint. In univariate analysis, group 2 stenosis was more likely to occur if the reconstruction performed was a CHP ($p = .01$). Management of the group 2 patients involved CO₂ laser incision and dilation of the stenotic segment. This was successful in 3 of the 7 group 2 patients. The other 4 patients in this group required permanent airway control in the form of either tracheostomy (3 patients) or permanent Montgomery T-tube placement (1 patient).

DISCUSSION

As reported in previous articles, SCPL should be viewed as a functionally and oncologically sound alternative to many more commonly used conservation laryngeal surgeries.¹⁻²³ However, as SCPL for selected endolaryngeal carcinoma gains wider acceptance, we as surgeons will begin to see more complications resulting from this type of partial laryngectomy and its various reconstructions.

Nontumoral, symptomatic laryngeal stenosis appears to be a rare complication of SCPL, with only 14 such patients (3.7%) in the present cohort of 376 consecutive patients who underwent SCPL at a single institution during a 20-year period. Such data are in line with the incidences reported in other series. Piquet and Chevalier,¹ in a series of 104 SCPL-CHEPs, noted laryngeal stenosis that required the placement of a Montgomery T-tube in 3 patients. De Vincentiis et al⁷ reported 5 permanent tracheotomies for dyspnea in a series of 70 patients managed with SCPL-CHP. Despite the low incidence of laryngeal stenosis, we believe that there are still some pitfalls that should be avoided when performing SCPL in order to reduce the incidence of this complication.

It is important to note that the most common cause of dyspnea and/or stridor after an initial period of successful decannulation after SCPL is local recurrence, which had a 6.7% incidence (25/376) in the present retrospective series. The availability of SCPL has reduced the indications for total laryngectomy in select "advanced" endolaryngeal cancers and has resulted in higher local control and long-term laryngeal preservation rates in select "early" endolaryngeal cancer.^{1-5,7-15} However, local recurrence does obviously occur after SCPL.²⁹ It is therefore imperative that all patients with symptomatic narrowing of the airway be thoroughly evaluated for the possibility of recurrence. In such cases, after imaging these patients, it is our routine to proceed with endoscopy

and, if indicated, biopsy of any suspicious areas.

The review of the medical charts in our series suggests that laryngeal stenosis after SCPL should be separated into 2 different groups. Group 1 consisted of immediate laryngeal stenosis in patients in whom decannulation could not be performed after operation because of insufficient restoration of the laryngeal airway. Seven such patients (1.85%) were noted in our series. Interestingly, the laryngeal stenosis in group 1 patients appeared mainly to be a result of technical errors made at the time of reconstruction. Three patients in group 1 managed with SCPL-CHEP had posterior prolapse of the epiglottis. This complication, in our opinion, results from inadequate placement of impaction sutures. In our opinion, the impaction sutures (we recommend No. 1 Vicryl) must travel in the submucosa of the epiglottis from the insertion of the suture toward the tip of the epiglottis and only then through the base of the tongue and around the hyoid bone. The SCPL-CHEP and SCPL-TCHEP procedures disrupt the lateral support of the epiglottis by dividing the pharyngoepiglottic folds. Therefore, if the impaction sutures fail to support the epiglottic cartilage in this fashion, the result is prolapse of the whole epiglottis backward over the airway. One patient developed synechiae between the vocal processes of the spared arytenoid cartilages. This complication was thought to be caused by an improper placement of the stitches that reposition both arytenoid cartilages once the thyroarytenoid muscles have been transected. The repositioning sutures (we recommend 3-0 Vicryl) should be tied to the cricoid in such a fashion that the arytenoid cartilages rock anteriorly on the cricoid, and so that they also rotate the vocal processes outward in order to "open" the posterior respiratory neoglottis. One patient had a ruptured pexis. This complication was caused by the No. 1 Vicryl sutures breaking through the cricoid cartilage. This complication, thought to be a result of too much tension at the level of the impaction line, can be avoided by performing a careful and extended dissection along the anterior tracheal wall to the level of the carina. This allows for complete mobilization of the airway upward and leads to a tension-free impaction. In the remaining 2 group 1 patients, no technical error could be identified, and excessive granulation tissue at the impaction line was thought to be the cause of the stenosis. In univariate analysis, no significant statistical relationship could be demonstrated between the development of group 1 stenosis and the variables under analysis. The management of group 1 patients involved the CO₂ laser to transect synechiae, resect the granulation tissue, incise redundant tissue, or resect a prolapsed epiglottis in 6 patients and revise the impaction in 1 patient who had

a rupture of the pexis. One of the 7 group 1 patients required multiple laser treatments over a 3-year period, and ultimately all attempts at decannulation failed. Five group 1 patients underwent successful decannulation without recurrence of the dyspnea, and 1 patient underwent completion laryngectomy.

Group 2 consisted of patients with delayed symptomatic laryngeal stenosis. In these 7 patients (1.85%), the development of dyspnea after an initial period of successful decannulation led to the diagnosis. Whereas stenosis in group 1 patients appeared to be caused, most likely, by technical errors made at the time of surgery, stenosis in group 2 patients seemed to result from the healing process and thus presented a much more difficult treatment problem. As the T-shaped neoglottis created in performing an SCPL heals, there can be a narrowing at the level of the cricohyoid impaction. It stands to reason that any factor that narrows the airway at the level of the impaction, such as an improper alignment between the hyoid bone and the cricoid cartilage or a smaller female larynx, or any factor that leads to more aggressive cicatricial formation, such as the use of preoperative or postoperative radiotherapy, diabetes mellitus, or gastroesophageal reflux, might predispose the patient to

postoperative narrowing. However, in our series, univariate analysis revealed none of these variables to be statistically relevant to the development of a delayed (group 2) stenosis. The only factor related to the development of stenosis in group 2 patients was the type of reconstruction performed, with stenosis being more likely to occur if the reconstruction performed was a CHP ($p = .01$); this finding might suggest a technical error in the form of an improper alignment of the cricoid cartilage and hyoid bone at the time of impaction. The management of group 2 patients involved CO₂ laser incisions and dilation of the stenotic segment. This, unfortunately, was much less rewarding than the management of group 1 patients. Multiple treatments and attempts to decannulate were often needed, and further, this regimen was successful in only 3 of the 7 group 2 patients. The 4 others in this group required permanent airway control in the form of either tracheostomy (3 patients) or permanent Montgomery T-tube placement.

In conclusion, the present retrospective series suggests that nontumoral stenosis after SCPL is a rare event that could be avoided by meticulous care at the time of surgery, because in most cases this complication appeared to be related to a technical error.

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SIXTH ASIAN RESEARCH SYMPOSIUM IN RHINOLOGY

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THYROID CARTILAGE AND VOCAL FOLD REDUCTION: A NEW PHONOSURGICAL METHOD FOR MALE-TO-FEMALE TRANSSEXUALS

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To date, there is a paucity of literature on surgery to alter vocal pitch in male-to-female transsexuals. The currently available pitch-raising surgical techniques yield neither a good long-term result nor a high enough pitch to simulate a female voice. We investigated a new procedure to alter vocal pitch in 6 male-to-female transsexuals. The principle is to shorten and increase tension on both vocal folds by composite resection of a vertical strip of the anterior thyroid cartilage along with a segment of vocal fold. This resulted in a satisfactory pitch alteration from an average of 147 Hz before operation to 315 Hz afterward. In addition to a marked pitch elevation, all patients were particularly pleased with the softness of the voice and the simultaneous loss of the prominentia laryngea (Adam's apple). The longest follow-up was 6 years. In conclusion, thyroid cartilage and vocal fold reduction is an effective method for long-term alteration of voice in male-to-female transsexuals.

KEY WORDS — male-to-female transsexual, phonosurgery, vocal fold, vocal pitch.

Since transsexualism has become accepted as a part of global society, a variety of medical and surgical approaches have become available for transsexuals, mainly for physical alteration to conform with their conceptual sex. Among these, male-to-female transsexual alteration has predominated over the reverse. Female hormones, in both oral and periodic parenteral forms, are widely used. It is widely believed that female hormones can make the skin finer and smoother, as well as enlarge the breasts and create a more female appearance. The most common surgical procedures requested from this group of people are blepharoplasty, eyebrow and eyelash micropigmentation, rhinoplasty, mandibular angle contouring, breast augmentation, shaping of the anterior prominence of the thyroid cartilage, and sex organ conversion. The combination of these procedures unquestionably can give patients a female appearance, but unfortunately, their masculine voice often embarrasses them in public. Nevertheless, voice or vocal pitch intervention is among the least common requests, simply because most are unaware of the availability of any technique.

There is a paucity of techniques relevant to vocal pitch conversion in male-to-female transsexuals in the literature. The current approach is aimed primarily at raising vocal pitch in female patients with abnormally low-pitched voices. The results are usually transient, as vocal pitch often returns to its original level over a period of time, and the original pitch

increase is not high enough to reach the female range. In addition, some techniques even accentuate the already prominent thyroid cartilage. This article reports on a new method to address these problems.

PATIENTS AND METHODS

From 1990 to 1996, 6 male-to-female transsexual patients, 20 to 27 years of age (mean, 23 years), were enrolled in this study. All patients were subjected to complete physical and psychological evaluation before operation. Five patients had undergone sex organ conversion, and all had been using estrogen and progesterone regularly (either orally or intramuscularly) for many years. Their general physical appearance was uniformly masculine except for the complexion, which appeared smooth, fine, and feminine. The anterior thyroid cartilage prominence (Adam's apple) of each patient was high and pointed, as is typical in men. The internal laryngeal structures, particularly the false and true vocal folds, were long, voluminous, and masculine. Most notably, their voices were masculine, in spite of voluntary female voice imitation, most obviously during coughing or sneezing. All patients were psychologically stable as assessed by a psychiatrist.

Objective voice assessments included preoperative and postoperative tape recording, spectrography, maximum phonation time, and determination of fundamental frequency (F0), jitter, and shimmer for sustained vowel /a/ using Visipitch M 3300 (Kay Ele-

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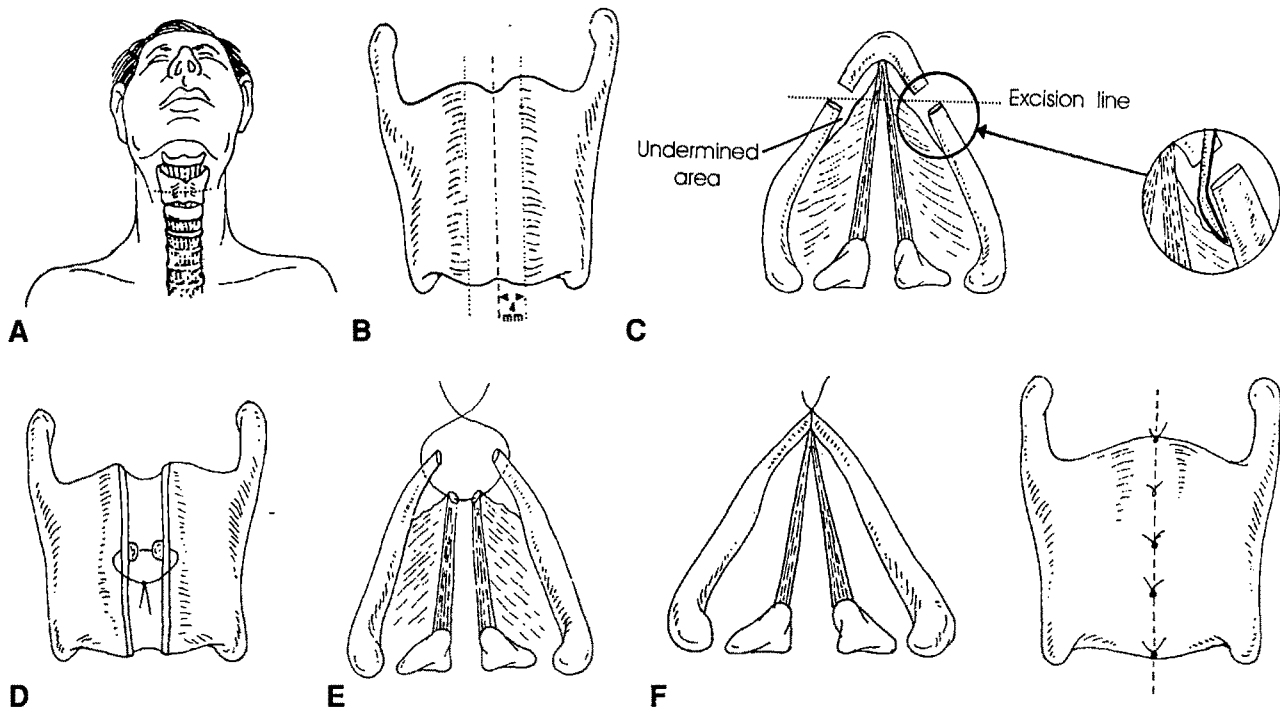


Fig 1. Technique. A) Skin incision. B) Thyroid cartilage incision. C) Undermining of inner perichondrium with composite resection of thyroid cartilage and vocal folds. D,E) Appearance of open-roof larynx and course of key suture in D) transverse view and E) coronal view. F) Final cartilage closure.

metrics, USA). Stroboscopic examination was not included in the assessments, because it was not available in our institution at the time of the study. Informed consent was obtained from all patients.

While under general anesthesia, the patient was placed in Rose's position. A 4- to 6-cm-long transverse cervical incision was made at the point halfway between the superior thyroid notch and the inferior border of the thyroid cartilage (Fig 1A). Superior and inferior skin flaps were then developed, the strap muscles were separated at the midline, and the thyroid cartilage was exposed. Without elevation of the outer perichondrium, parallel vertical cuts were made on the sides of the thyroid alae at a point 4 mm away from the midline or the anterior commissure, running from the superior border down to the inferior border of the thyroid cartilage (Fig 1B). This step could be carried out with a scalpel; on rare occasions, an oscillating saw was required. A strip of cartilage with Broyle's ligament attached to it was then obtained and pulled forward, exposing the inner perichondrium and the vocal ligament. From the posterior remaining portion of thyroid cartilage, a minimal (3 to 4 mm) backward undermining of the inner perichondrium with overlying soft tissue and vocal folds at this stage facilitated stretching of the folds. The act of pulling the vocal folds taut before cutting is critical, because it enables a longer segment of vocal fold than of the anterior thyroid cartilage commis-

sure to be excised. The vocal folds were then cut bilaterally, so that the excised piece of tissue was composed of anterior thyroid cartilage with the attached Broyle's ligament and the anterior part of the vocal folds (Fig 1C). The length of vocal fold to be excised was approximately 6 mm on each side, which was approximately 2 mm longer than the excised anterior thyroid cartilage. At this step, an "open-roof" larynx was obtained; the perforation was about 5 mm wide, and the vertical length involved the entire length of the thyroid cartilage from the superior border to the inferior border (Fig 1D,E). The cut ends of the retaining alar cartilages were then reapproximated. Closure was accomplished by using 3-0 nylon or Prolene, with the initial key suture placed at the vocal fold level so that the bite included both cut ends of the remaining thyroid cartilage with its attached perichondrium and the vocal folds, forming a new anterior commissure; another 1 or 2 interrupted sutures placed both above and below the key suture were usually sufficient to stabilize the foreshortened larynx. One should avoid traumatizing the cut ends of the vocal folds by holding the forceps gently. The force applied to tie the knot should be just enough to approximate both vocal folds and cartilages; if too tight, the force may cause cutting through tissue. Care should be taken to minimize exposure of the key suture into the laryngeal lumen; this can be done by passing the suture through the wound only and never through the mucosa of the vocal folds (Fig 1E). In

RESULTS OF TREATMENT

Case	Age (y)	MPT (s)		Jitter (%)		Shimmer (dB)		Pitch (Hz)		Follow-up (mo)
		Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	
1	25	17	16	2.05	1.23	0.94	0.75	120	283	72
2	20	17	16	3.05	0.55	0.84	0.69	162	264	62
3	27	16	15	1.13	0.62	0.75	0.59	100	420	67
4	22	12	10	0.55	0.35	0.65	0.58	165	350	24
5	21	14	12	0.31	1.10	0.53	0.73	164	273	12
6	23	13	12	7.03	2.08	1.23	0.80	172	300	5

MPT — maximum phonation time.

some cases, however, the thyroarytenoid muscle was too friable to hold the suture; the bite in such cases may include the mucosa, so that a minute portion of the key suture is exposed in the air lumen. The strap muscles were reapproximated at the midline, and subcutaneous and skin closure was made layer by layer over a small Penrose drain. The patients were instructed to rest their voices for at least 2 weeks, and antitussive medication was routinely prescribed for at least 1 week. Follow-up was made every 2 weeks for the first month after operation, and every 1 or 2 months thereafter.

RESULTS

Subjectively, all 6 patients were satisfied with their new voices and were particularly pleased with the softness of the altered vocal tone. One patient left the country, and another patient failed to attend the follow-up; only early postoperative results were obtained (5 and 12 months). The patients' voices were almost feminine at the last follow-up. Four patients maintained a female range of vocal pitch at 2 to 6 years of follow-up. The preoperative F₀ and postoperative F₀ were 100 to 172 Hz (mean, 147 Hz) and 264 to 420 Hz (mean, 315 Hz), respectively. The mean preoperative and postoperative values for jitter were 2.35% and 0.98%, respectively, and the mean preoperative and postoperative values for shimmer were 0.82 dB and 0.69 dB, respectively. The mean

preoperative and postoperative maximum phonation times were 15 and 14 seconds, respectively. The results are summarized in the Table. Figure 2 demonstrates a sample of preoperative and postoperative spectrograms from 1 patient. Figure 3 demonstrates a sample of the postoperative endoscopic appearance of the vocal folds.

In 2 patients, granulation tissue developed at the anterior commissure 1 to 2 months after the operation. One session of carbon dioxide laser vaporization via a microlaryngoscopic approach was sufficient for the removal of granulation tissue.

DISCUSSION

Currently, there are only a few well-documented methods of raising vocal pitch, namely, cricothyroid approximation, vocal fold webbing, vocal ligament tightening, and partial thyroarytenoid myectomy.

Cricothyroid approximation was the first procedure ever described to alter vocal pitch. As the name implies, it involves bringing the thyroid and cricoid cartilages together by suturing, and keeping the vocal folds in tension, thus elevating the vocal pitch. This method was introduced in 2 patients by Isshiki et al¹ in 1974; in 1983, a larger series of another 11 patients was published.² The primary indication in both series was androphonia in women. However, the pitch increase using this approach was often in-

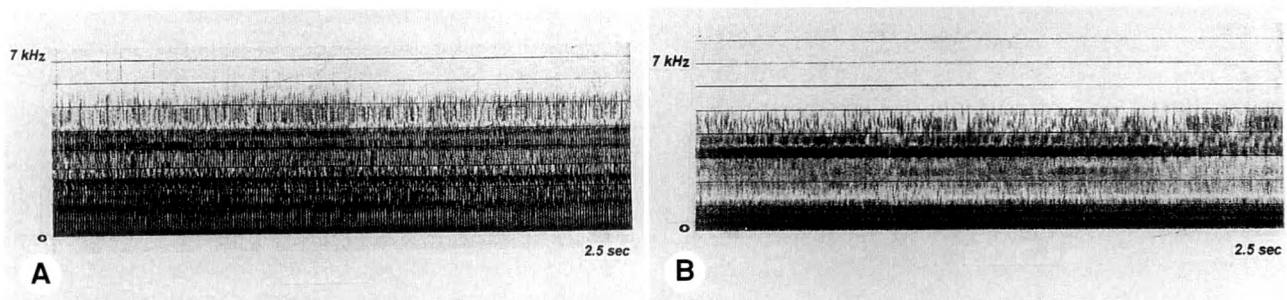


Fig 2. Sample of spectrograms from 1 patient. A) Preoperative spectrogram of sustained vowel /a/ demonstrates noise components between vowel formants with noise energy above 5,000 Hz, representing hoarseness in phonation, which may be attributed to vocal strain as result of voluntary falsetto voice production. Less-frequent striations signify low fundamental frequency. B) One year after operation, there was reduction in noise components, designating improved voice quality, which may be secondary to elimination of vocal strain. Note higher fundamental frequency, demonstrated by increase in rate of striations.



Fig 3. One year after operation, vocal fold configuration appeared normal, except for minimal scar at anterior commissure. There was no web formation; vocal fold movement was normal.

sufficient and was often accompanied by regression as a result of inevitable suture loosening.³ Sataloff et al⁴ proposed that cricothyroid fusion, a modification of the previous technique, might provide a better long-term result.

The vocal fold webbing technique can be performed either endoscopically, as introduced in Germany, or by an external laryngofissure approach, as described by Donald.⁵ The principle was to create an anterior commissure web one third the length of the vocal fold. Although some improvement in pitch was observed, most patients had a raspy or breathy voice.

The vocal ligament tightening technique was developed by LeJeune et al.^{6,7} The principle of this procedure was also to increase vocal fold tension. This was accomplished by creating an inferiorly based rectangular or triangular flap on the anterior thyroid cartilage to which Broyle's ligament remained attached. This flap was then pulled forward and secured in place by a tantalum shim. These procedures were performed in patients whose thyroarytenoid ligaments had lost tension because of either trauma or idiopathy. The early results were encouraging, although not uniform, but the long-term results are not known. On the basis of the same mechanism, Tucker⁸ proposed a superiorly based flap, which turned out to have a better result because of greater anterior displacement. He performed this procedure in 8 patients who had vocal fold flaccidity. All patients experienced immediate improvement, but only 3 maintained improvement beyond 6 months.³

Partial thyroarytenoid myectomy (demonstrated in animals) has been claimed to be a safe method to reduce the vocal fold mass.⁹ It may have a potential adjunctive role in pitch-raising surgery. Abitbol, in Paris, applied this technique, using a laser to remove

the belly of the thyroarytenoid muscle. His patients noted elevation of pitch with slight breathiness (R. T. Sataloff, personal communication, 1999).

These methods are capable of raising the vocal pitch to some extent, but not to that of the female vocal range. To best understand the physiological factors that influence vocal pitch, one should be reminded of the following formula¹⁰: $F_0 = (1/2L)\sqrt{T/P}$, where L is the length of the vocal folds, T is the mean longitudinal stress, and P is the tissue density.

It is clearly demonstrated from this formula that vocal pitch will be raised if one can achieve the following: 1) shorten or decrease the total mass of the vocal ligaments, 2) increase the tension of the vocal folds, or 3) obtain a combination of these for best results. The mechanism of the previously mentioned techniques is related to only one of these factors, ie, increase in the tension or reduction in the mass of the vocal fold. Proctor¹¹ described how increases in tension cause thinning of the vocal fold; however, by this means there is no actual decrease in the total vocal fold mass. Thus, it is still the tension alone that accounts for the increase in vocal pitch in the previous techniques. This may explain why the rise in vocal pitch is inadequate.

In our study, the thyroid cartilage was incised first, and parts of the vocal folds were excised while being stretched; these were removed en bloc with the intention of leaving the remaining vocal folds shorter than the anteroposterior diameter of the thyroid cartilage, resulting in shortening and tightening the vocal fold and decreasing the vocal mass at the same time. Thereby, all factors necessary for raising vocal pitch have been addressed. Furthermore, a consequence of excising the anterior portion of the thyroid cartilage is the patient's satisfaction from gaining a more female appearance by losing the thyroid cartilage prominence. In contrast, the previously mentioned vocal fold pulling techniques cannot alter the appearance in such a way. It was interesting to note that none of the patients in this study had an abnormally high audible voice despite a resultant average F_0 that was apparently too high.

There are 2 inherent disadvantages of our technique. First, it is performed with the patient under general anesthesia; therefore, subjective voice monitoring or testing is not possible. The length of vocal fold to be excised thus depends on an estimation rather than being adjusted by voice monitoring.

Second, it is an invasive technique, involving an alteration of the delicate internal laryngeal structures. Although the result was satisfactory, further refinement of the surgical technique is required, particu-

larly on the length of vocal fold to be excised to attain the best outcome. The technique is not recommended in professional singers, because of the risk of altering voice quality.

To solve some of these problems, we are currently performing this procedure with a local anesthetic. Intraoperative patient acoustic feedback enables a more precise excision of the vocal folds. However, the initial results have not shown any significant difference from those obtained with the technique presented herein. The final long-term results will be presented in a future report.

The incidence of anterior commissure granulations in this series probably reflects a learning curve, as they occurred only in the initial 2 cases (2 of 6, or 33.3%). The cause of these granulations may have been exposure of the suture into the laryngeal lumen, as seen during postoperative endoscopic examination. There seems to be no evidence of loosening of the connection between the anterior commissure and the thyroid cartilage.

Voice therapy may play an important role both before and after operation. Before the operation, the patient may be given training in a technique of voluntary vocal pitch elevation, and on other speech pat-

terns and vocal behaviors important to gender identification. After the operation, voice quality or efficiency may be further improved by voice therapy.¹² Unfortunately, the patients' compliance with voice therapy in this series was very poor. Vocal gender identification involves a great deal more than simply a rise in vocal pitch. The differences in the configuration of the vocal tract and resonators between men and women are important in contributing to the overall vocal distinguishability. Surgical alteration of the vocal folds is feasible, but an appropriate surgical technique to affect the vocal resonators is probably less so. However, special vocal training may favorably modify tongue carriage to effect a change in formant frequency. A careful and thorough preoperative examination should be done, and adequate information on the benefits and risks of surgery should be given to the patient before obtaining informed consent.

CONCLUSION

Thyroid cartilage and vocal fold reduction, a new method of raising vocal pitch in male transsexuals, involves composite excision of the anterior commissure. A long-lasting alteration of vocal pitch to one in the female range is accomplished with satisfactory voice quality.

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IMAGING CASE STUDY OF THE MONTH

KILLIAN-JAMIESON DIVERTICULUM: A CASE REPORT AND A REVIEW OF THE LITERATURE

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INTRODUCTION

The Killian-Jamieson (KJ) diverticulum is a rarely encountered type of hypopharyngeal diverticulum, and there are very few reports describing this entity.^{1,2} The KJ diverticulum arises between the fibers of the cricopharyngeus muscle superiorly, and the esophageal muscle fibers inferiorly, in an area known as the Killian-Jamieson (KJ) area (Fig 1). This site of herniation is below that of the much more common Zenker's diverticulum, which arises between the fibers of the cricopharyngeus muscle inferiorly and the fibers of the inferior constrictor muscle superiorly, through an area known as Killian's triangle. Clinically, the 2 diverticula may present in a similar fashion. However, radiographic studies can assist the phy-

sician in determining the type of diverticulum before operation. The barium esophagram and, in particular, axial computed tomography (CT) scans can localize the origin of the sac and help determine the type of diverticulum.

In this report, we present a case of KJ diverticulum and review the clinical presentation, differential diagnosis, and radiographic findings that distinguish this entity from the more common Zenker's diverticulum. We also discuss the importance of recognition of this entity before surgical excision because of its intimate relationship with the recurrent laryngeal nerve.

CASE REPORT

A 53-year-old woman presented to the University of California, Irvine, otolaryngology-head and neck surgery clinic with complaints of dysphagia for solids and liquids, hoarseness, and a 9-kg (20-lb) weight loss over a 6-month period. She had previously been in good health. Her social history was significant for a 30-pack-year history of cigarette smoking and heavy alcohol use. A head and neck examination was remarkable only for the laryngeal and neck examination findings. A laryngeal examination revealed normal-appearing supraglottic mucosa and mobile true vocal cords without mucosal lesions. The postcricoid mucosa was swollen and erythematous, with a granular appearance. Examination of the neck revealed a subtle, soft, and diffuse lower left anterior neck swelling. Palpation of this area deflated the swelling, with production of an accompanying gurgling sound emanating from the pharynx. The patient was given omeprazole to control gastroesophageal reflux symptoms, and a barium contrast esophagram and a CT scan of the neck with contrast were obtained.

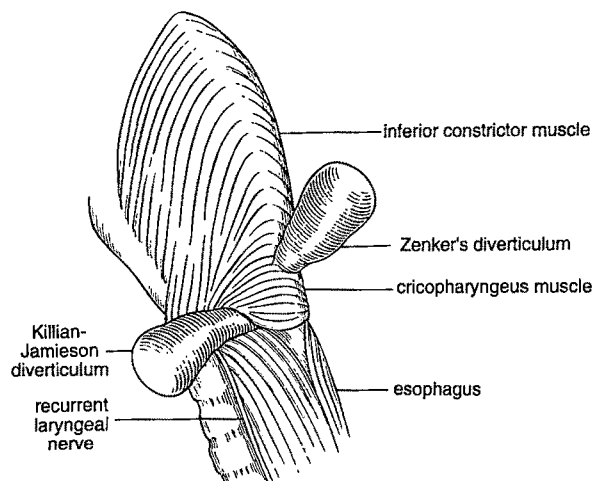


Fig 1. Posterolateral view of hypopharynx and cervical esophagus. Anatomic locations of Zenker's diverticula and Killian-Jamieson diverticula are depicted to emphasize more inferior and lateral origin of Killian-Jamieson diverticula, and close proximity of origin of sac to recurrent laryngeal nerve.

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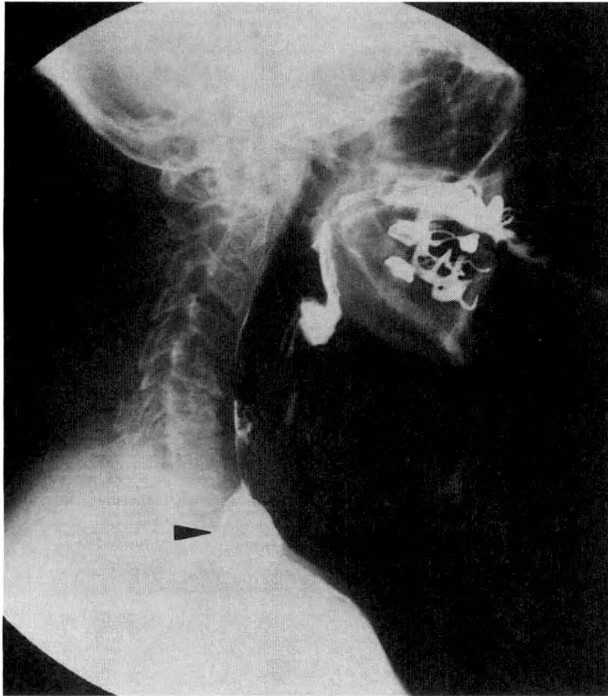


Fig 2. Barium contrast esophagram of patient with Killian-Jamieson diverticulum. Lateral view of neck and upper chest after oral ingestion of barium contrast material. Large sac is demonstrated at level of first and second thoracic vertebrae. There is no cricopharyngeal bar demonstrated, and very little posterior extension of sac is demonstrated. Arrowhead indicates diverticulum.

The contrast esophagram shown in Fig 2 reveals a large sac lying just above the thoracic inlet. No cricopharyngeal bar is visualized, and the sac does not project in a posterior direction. An axial CT scan of the neck (Fig 3) demonstrated a left-sided, air-filled diverticulum arising below the level of the cricoid cartilage and slightly displacing the esophagus to the right. The primarily lateral extension of the diverticulum, absence of a cricopharyngeal bar, and inferior location of the sac origin defined by the CT scan favored the presence of a KJ diverticulum. The patient subsequently elected to undergo transcutaneous excision of the diverticulum and cricopharyngeal myotomy. Rigid esophagoscopy demonstrated a wide-mouthed, laterally based sac filled with undigested food particles and arising at the esophageal inlet. The sac contents were removed, and the diverticulum was packed with gauze to assist identification of the sac during excision.

The diverticulum was approached through a horizontal left neck incision, and the sac was mobilized after identification and preservation of the recurrent laryngeal nerve under the thyroid gland. The sac originated below the cricopharyngeus muscle, immediately (<3 mm) posterior and superior to the recurrent laryngeal nerve. The relationship between the sac and the recurrent nerve is shown in Fig 4. The diverticu-

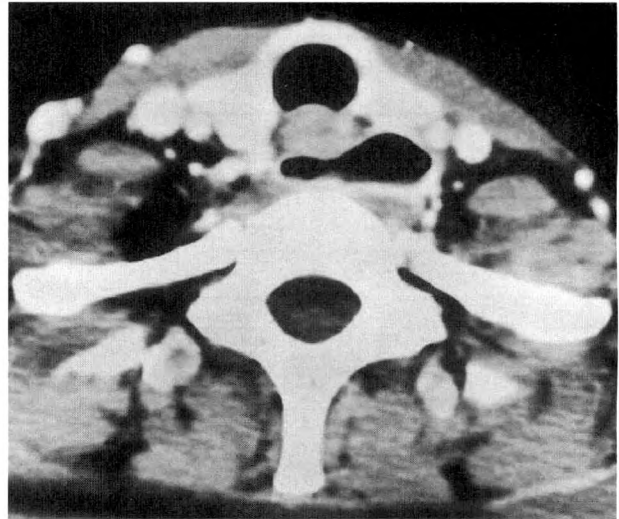


Fig 3. Axial computed tomogram of patient shown in Fig 2. Large, air-filled sac is demonstrated, primarily lateral to esophagus, at level of first thoracic vertebra. Thin rim of enhancement surrounds air-filled sac, and there is no evidence of underlying tumor or cervical adenopathy.

lum was transected with a surgical stapling device, and the wound was irrigated and closed in layers with placement of a suction drain. The patient tolerated a clear liquid diet on postoperative day 1 and a soft diet on postoperative day 3. A barium contrast esophagram obtained 1 week after surgery did not demonstrate any leak or stricture. Two years after surgery, the patient remained free of symptoms and was tolerating a regular diet, but was unwilling to undergo a repeat contrast study to document the long-term outcome.

DISCUSSION

Although Ludlow was the first to describe the hy-



Fig 4. Intraoperative view of Killian-Jamieson diverticulum. Diverticulum sac is shown retracted superiorly on right side of figure. Left thyroid lobe has been mobilized anteriorly, and left recurrent laryngeal nerve lies directly adjacent to diverticulum sac (delineated with arrowhead and surgical instrument).

popharyngeal diverticulum in 1769, it was Friedrich von Zenker, a Professor of Pathology at Erlangen University, who listed all previously reported cases and gave a detailed clinical and pathological description, whose eponym was assigned to this entity.¹ In 1877, Zenker described 34 patients with a protrusion of the pharyngeal mucosa in the dorsal wall of the pharynx at the junction between the hypopharynx and the esophagus.² He also described the difference between pulsion and traction diverticula. Although there has been considerable investigation to determine the cause of pulsion diverticula of the hypopharynx, there is still debate about their pathophysiological mechanism. Most authors believe, because of the age distribution of hypopharyngeal diverticula, that a congenital weakness in the pharyngeal musculature is unlikely and that the lesions are acquired. The mechanism for their development is not completely understood. Dyscoordination of the pharyngeal constrictors, cricopharyngeal spasm, failure of relaxation of the sphincter, and premature contraction have all been implicated, but manometric and radiographic studies have failed to conclusively determine the pathophysiological mechanism leading to development of the diverticulum.³⁻⁵ Gastroesophageal reflux disease is seen more commonly in those with hypopharyngeal diverticula, but its contribution is unclear.

The vast majority of articles about hypopharyngeal diverticula have concentrated on posterior (Zenker's) diverticula. Much less emphasis has been placed on lateral (KJ) diverticula. Moynihan² described a lateral diverticulum arising from the KJ area between the fibers of the cricopharyngeus muscle superiorly and the circular fibers of the esophagus inferiorly. Subsequently, Moersch and Judd⁶ reported on this entity, and Shallow⁷ reported lateral diverticula to be relatively common (up to 35% of hypopharyngeal diverticula). This finding is supported by Ekberg and Wahlgren,⁸ who performed cineradiography studies on 854 patients with dysphagia in Malmö, Sweden. In their series, they identified 20 Zenker's diverticula and 16 KJ diverticula. These reports indicate that lateral diverticula often are unrecognized and erroneously classified as Zenker's diverticula.

Cadaveric studies define the KJ diverticulum as arising inferior and lateral to the Zenker's diverticulum.⁴ Zenker's diverticula exit the pharynx posteriorly through an area of muscular weakness between the inferior constrictor muscle fibers superiorly and the transverse fibers of the cricopharyngeus muscle inferiorly, at an area commonly referred to as Killian's dehiscence. In contrast, the origin of the KJ diverticulum lies inferior to the transverse fibers of the cricopharyngeus muscle and superior to the longitudinal muscular fibers of the proximal esophagus,

in a lateral position just behind the cricothyroid joint region. This area corresponds to the entry point of the recurrent laryngeal nerve into the larynx.

Zenker's and KJ diverticula may have identical clinical presentations. Accurate differentiation between Zenker's and KJ diverticula relies on radiographic studies, specifically, barium contrast esophagography and axial CT scanning of the neck. It is important to evaluate both the anteroposterior and lateral projections while the patient is supine and erect during the swallowing study. Wide-based hypopharyngeal diverticula may be overlooked if all positions are not evaluated.⁵ Several characteristics of the barium swallow results point to the presence of a KJ diverticulum. Whereas the neck of the Zenker's diverticulum generally presents posteriorly, with a prominent cricopharyngeal bar often identified below the sac, the KJ diverticulum extends laterally, below the cricopharyngeal muscle fibers. On an anteroposterior view, Zenker's diverticula will show little lateral projection compared to KJ diverticula. On a lateral view, Zenker's diverticula will often demonstrate a prominent cricopharyngeal bar and posterior extension of the sac in relation to the esophagus, which are not seen with KJ diverticula. Although contrast esophagography can provide diagnostic information, it often cannot definitively distinguish between the 2 types of diverticula, especially when the pouches have become very large and extend inferiorly. Often, when Zenker's diverticula acquire such a large size, they extend laterally and are difficult to differentiate from KJ diverticula.

More precise localization of the origin of a diverticulum can be obtained with an axial CT scan of the neck. A CT scan demonstrates a laterally projecting sac with the origin below the level of the cricoid cartilage. Zenker's diverticula will arise at a higher level and demonstrate a more-posterior sac orientation. A second advantage of CT scanning is the ability to identify an occult malignancy arising in the wall of a long-standing diverticulum, the incidence of which has been reported to be 0.4%.⁹

Reports of surgical management of hypopharyngeal diverticula have focused exclusively on management of Zenker's diverticula. Zenker's diverticula may be surgically treated by external techniques or an endoscopic internal approach. A number of external approaches are available. Very small diverticula may be treated with cricopharyngeal myotomy alone. Sac suspension has been used for very debilitated patients who cannot withstand a more extensive surgical procedure. The most commonly used external technique is sac excision with cricopharyngeal myotomy.¹⁰ Use of a surgical stapler to transect

and close the pharyngotomy has been described, with good results.^{11,12} Inversion of the diverticulum with myotomy has also been advocated for small diverticula.^{13,14}

Endoscopic management has been gaining wider acceptance, and a number of series have reported equal or better results, with minimal complications. Although Mosher was the first to describe the endoscopic treatment of a hypopharyngeal diverticulum in 1917, the first major series was not reported until 1960, by Dohlman and Mattsson.¹⁵ They published results of 100 cases treated endoscopically, further described the endoscopic technique, and developed a special set of instruments that allowed exposure of the party wall between the esophagus and the diverticulum sac for division by electrocautery. They attained symptomatic improvement in more than 90% of their patients, with only a 7% incidence of residual diverticula. More recent modifications to the technique include incorporation of the CO₂ or potassium titanyl phosphate laser, and use of an endoscopic stapling device to divide and ligate the party wall of the diverticulum.^{14,16-20}

Endoscopic treatment of posterior diverticula relies on disrupting the fibers of the cricopharyngeus muscle and thereby opening the neck of the sac to allow drainage into the esophagus. Dissection is carried out in the posterior midline, well away from the recurrent laryngeal nerve.²⁰ There are important anatomic differences between posterior and lateral hypopharyngeal diverticula.²¹ First, the site of origin of a lateral diverticulum is at a lower vertical level (below the cricopharyngeus muscle) than that of the posterior diverticula. Second, the lateral origin through the KJ area is directly adjacent to the entry point of the recurrent laryngeal nerve into the larynx. Because of the differing anatomic location of the lateral diverticula, endoscopic management could present significant inherent risk to the recurrent laryngeal nerve. For these reasons, we selected an external approach to treat the case presented. Operative findings validated our concerns, demonstrating the recurrent laryngeal nerve lying within 3 mm of the inferior portion of the proximal neck of the sac and requiring meticulous dissection to be separated from the sac wall.

Although lateral diverticula have been demonstrated to be relatively common on radiographic studies, very little literature concerning this entity exists when compared to that for posterior (Zenker's) diverticula. It is possible that many lateral diverticula are diagnosed as Zenker's diverticula and managed as such. Contrast radiography can often distinguish between posterior and lateral diverticula, but CT evaluation may be necessary to better define the site of origin of the laterally oriented diverticulum, and in the case presented, it was helpful in delineating the anatomy before operation.

If external surgical management with recurrent nerve identification is planned from the outset, the precise anatomic origin of the diverticulum is less critical, because the relevant anatomy will be delineated at the time of resection. If, however, an endoscopic approach is contemplated, diverticula originating in the lateral KJ area could have a higher likelihood of causing recurrent laryngeal nerve injury if they are treated endoscopically. It is also possible that very large, wide-mouthed lateral diverticula could extend in a posterior direction, mimicking the appearance of classic posterior diverticula, and that safe posterior division could be done.

CONCLUSION

A KJ diverticulum is an uncommon and underrecognized type of hypopharyngeal diverticulum. Its site of origin is more inferior and lateral than that of the well-recognized Zenker's diverticulum. Their clinical presentation does not distinguish between the 2 entities, but radiographic findings of a laterally based diverticulum and CT localization of the origin of the sac below the cricoid cartilage can provide an accurate diagnosis of a KJ diverticulum. Because of the intimate relationship of the sac to the recurrent laryngeal nerve, we are concerned about possible recurrent laryngeal nerve injury with attempted endoscopic treatment, and we advocate external sac excision after definitive identification of the recurrent laryngeal nerve. However, definitive recommendations cannot be made on the basis of our single case, and we provide this report to increase awareness of the KJ diverticulum and stimulate discussion of its diagnosis and management.

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BOOK REVIEWS

Pathogenesis in Cholesteatoma

Bernard M. P. J. Ars, ed. Soft cover, illustrated, 164 pages, 1999. Kugler Publications, The Hague, the Netherlands, \$54.

Purpose: To present a critical and contemporary evaluation of cholesteatoma and to provide information that hopefully will lead to further advancement in treatment. The book focuses solely on the mechanisms of the genesis of this disease and, as such, has been set up as an informative work of analysis and reference intended for use in fundamental and applied research or as an educational tool.

Contents: There are 9 chapters that make up this book, and the first 6 deal solely with the pathogenesis of cholesteatoma. The last 3 chapters deal with various aspects of anatomy such as examination of the nasopharynx, the role of the supratubal recess in cholesteatoma pathogenesis, and the malpneumatization theory of acquired cholesteatoma.

Attributes and Limitations: The contents of this book were formulated from the editor's interest and research; it is a comprehensive and updated survey of the study of cholesteatoma. The chapters provide a complete source of the most up-to-date information on the basic science and pathology of cholesteatoma. In addition, new areas of experimental and/or clinical investigation are included.

Applicability: This book offers the otolaryngologist a unique opportunity to improve and update his or her knowledge of modern trends in the study of the genesis of cholesteatoma.

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Felix Semon 1849-1921. A Victorian Laryngologist

Donald Harrison. Hard cover, illustrated, indexed, 243 pages, 2000. Royal Society of Medicine Press, London, England, £20.

Purpose: To convey a critical reappraisal of Felix Semon's life and times based on detailed research of documents, sources, and various organizations and societies. One source is an autobiography of Felix Semon that was published approximately 5 years after his death.

Contents: There are 12 chapters and a list of illustrations. The chapters can be divided into sections on Semon's early life, music, and marriage, including royal connections. Section 2 involves his professional life. Section 3 discusses his retirement, especially his travels around the world. Another chapter is a very interesting section on Morrell MacKenzie and the Crown Prince of Prussia. Semon took the position of criticizing MacKenzie for not recognizing that the Crown Prince's lesion was growing right before him despite the fact that the biopsy results were negative and that it was obviously a cancer.

Attributes and Limitations: It can be said of Felix Semon that during most of his life he surrounded himself with important people, especially royalty. He moved with his family from Danzig, where he was born, to Berlin when he was 3 years old. He served with the Prussian Uhlan Guards in the Franco-Prussian War. When his regiment returned to Berlin, they marched into the city playing the "St Quentin March," composed by Semon. He was a personal friend to the sons of Count Bismarck. His medical training took place in Berlin under such great teachers as Virchow and Traube. (Virchow remained a personal friend.) His postgraduate study was with Morrell MacKenzie in London. Remaining in London, Semon became one of the most out-

standing laryngologists of all time and is mainly remembered now for "Semon's Law": in progressive organic diseases of the motor laryngeal nerves, the abductors of the vocal cords (posterior cricoarytenoids) are the first, and occasionally the only, muscles affected. I had thought that he introduced and developed the modern operation for laryngofissure for early cancer of the larynx, but the author states that his role was primarily as a medical clinician, in that his main contribution to this procedure (laryngofissure) was to summarize his indications for the surgery.

Semon and his famous singer wife, Augusta Redeker, made their home a renowned social center for musical entertainment. Many members of the British aristocracy were their friends. The author makes a strong case that Felix Semon was instrumental in laryngology's being accepted its own right as a separate discipline after the stigma left by Morrell MacKenzie regarding the death of the Crown Prince.

Applicability: The text is valuable as a historical reference for laryngologists and, indeed, for all physicians and students of medicine.

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Acoustic Neuroma: Trends and Controversies

Robert Filipo and Maurizio Barbara, eds. Soft cover, illustrated, 175 pages, 1999. Kugler Publications, The Hague, the Netherlands, \$54.

Purpose: Directed to young otologists who are keen on approaching the problems of acoustic neuroma, as well as to experienced specialists as a review.

Contents: The book is divided into 5 sections, which include generalities (experience and incidents); diagnostics (imaging, audiological correlations); monitoring (facial nerve); monitoring (hearing); and treatment (includes surgical technique, although not in depth). This subject matter is taken from the proceedings of the symposium Acoustic Neuroma: Trends and Controversies, held in Rome, Italy, November 13-15, 1997.

Attributes and Limitations: This book represents a critical and contemporary evaluation of the situation of acoustic neuroma. The book clearly shows that there are specific approaches to meet the needs of the patient. That is to say, when the hearing is poor, a translabyrinthine approach should be used, and to preserve hearing, middle fossa and suboccipital approaches should be used. At times, there may be no surgical treatment necessary at all — merely careful observation.

There are no new challenges represented in this small volume, and no positive, realistic, new contributions to the topic. The increase in stimulus rate mentioned on page 50 as a recent advance was introduced in 1977 by Don, Allen, and Starr. The test is based on increase in stimulus rate to 90 clicks per second. Wave V latency increases by approximately 0.5 milliseconds in normal subjects when the stimulus rate is increased from 10 stimuli per second to 100 stimuli per second. Increases of wave V latency at fast rates over slow rates of more than 0.7 to 0.8 milliseconds are considered abnormal (Hood and Berlin, 1986).

Applicability: It is a good, up-to-date review of the features of acoustic neuroma, and is recommended to students and to otologists who deal in surgery of the lesion.

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PROTO-ONCOGENE RAF-1 AS AN AUTOANTIGEN IN MENIERE'S DISEASE

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The 28 kd protein extracted from the guinea pig inner ear membranous fraction, which reacted with sera from patients with Meniere's disease, has been subjected to microsequencing. Nineteen amino acids were obtained (IVQQFGFQRRASDDGKLTQ). A protein data bank search showed that this sequence corresponded to residues 41 to 60 of human Raf-1 protein. Sera from 16 of 27 patients with Meniere's disease showed reactivity to the recombinant purified glutathione-S-transferase-Raf-1 protein. These results support the hypothesis that a subgroup of patients who suffer from Meniere's disease, as well as some other kinds of autoimmune inner ear diseases, have an autoantibody against Raf-1 protein.

KEY WORDS — inner ear disease, 28 kd protein, Meniere's disease, Raf-1 protein.

INTRODUCTION

A number of serologic studies have implicated autoimmunity in inner ear diseases. A common strategy is to determine the autoantigen. Extracted proteins from the inner ear tissues of humans, guinea pigs, rabbits, cows, chicks, and pigs have been used to identify the autoantigens involved in inner ear diseases. Several potential antigens have been reported to react with sera from patients with inner ear disease and diagnoses of Meniere's disease, idiopathic progressive bilateral sensorineural hearing loss (IPBSNHL), otosclerosis, and sudden hearing loss.¹⁻⁹ Among these potential autoantigens, a 30 kd protein from the human inner ear extracted proteins has been reported to react with sera from patients with Meniere's disease.⁴ Cao et al⁸ have found that patients with inner ear disease have antibodies against a 30 kd protein extracted from the guinea pig inner ear. This 30 kd protein is extremely abundant in the modiolus pool and the organ of Corti, but not in the spiral ligament or stria vascularis of the inner ear.⁸ Cao et al⁹ have identified this 30 kd protein as a myelin protein PO derived from the acoustic nerve and spiral ganglion. In a previous investigation, we reported that a 28 kd protein from the guinea pig inner ear membrane fraction strongly reacted with sera from patients with Meniere's disease.¹⁰ This 28 kd protein appeared in the

membranous fraction (containing the basement membrane, organ of Corti, stria vascularis, spiral ligament, and vestibular epithelium), but not in the neural part (containing the spiral ganglion and cochlear nerve in the modiolus, and the vestibular nerve in the temporal bone) of the inner ear.¹⁰ In this study, we purified this 28 kd protein and identified it as the Raf-1 protein.

MATERIALS AND METHODS

Animals. Hartley strain female guinea pigs were purchased from Sasco Co (Wilmington, Mass).

Patient Selection. Sera from 27 patients with Meniere's disease were supplied courtesy of Drs J. Bernstein and Y. Yazawa. The diagnosis of Meniere's disease was based on the American Academy of Otolaryngology-Head and Neck Surgery criteria.¹¹ All of the patients with Meniere's disease were symptomatic. The sera used in the present study were stored at -20°C.

Preparation of Extracted Proteins From Guinea Pigs. The preparation of extracted proteins from the membranous or neural fraction of retrocochlear, facial nerve, or brain tissue has been described previously.¹⁰ Briefly, tissues were obtained from 40 Hartley strain female guinea pigs (300 to 320 g). The guinea pigs were deeply anesthetized (intraperitone-

From the Division of Allergy and Immunology, Department of Medicine, University of Tennessee, Memphis, Tennessee (all authors). Dr Cheng is now with Johnson and Johnson Pharmaceutical Company, Raritan, New Jersey. This study was supported in part by the UTMG Allergy Support Fund and National Institutes of Health grant DC00652-04A3. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Tennessee.

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neal injection of a mixture of ketamine 40 mg/kg and xylazine 10 mg/kg) and perfused with 0.01-mol/L phosphate buffered saline solution (pH 7.4; PBS) through the left ventricle. Both temporal bones were removed and kept in crushed ice. The membranous part of the inner ear (basilar membrane, organ of Corti, stria vascularis, spiral ligament, and vestibular epithelium) and the neural part of the inner ear (the spiral ganglion and cochlear nerve in the modiolus, and the vestibular nerve in the temporal bone) were dissected under a microscope. Tissues from the facial nerve and brain were also obtained from the animals. These tissues were sonicated for 20 seconds (Sonifier cell disrupter model w-185, Heatsystems-Ultrasonics, Inc, Wake Forest, NC) in a lysis buffer (100-mmol/L sodium chloride [NaCl], 10-mmol/L Tris buffer, pH 7.6, 1-mmol/L ethylenediaminetetraacetate, pH 8.0, 0.1% sodium dodecyl sulfate [SDS], 1% Nonidet P-40, 2 µg/mL aprotinin, 100 mg/mL phenylmethylsulfonyl fluoride). The extracted proteins were incubated at 0°C for 30 minutes and centrifuged at 10,000 rpm for 10 minutes. The supernatant was filtered through a 0.22-µm filter (Millipore Co, Bedford, Mass), boiled in water for 5 minutes, and then stored at -80°C.

Preparation of Recombinant GST-Raf-1 Protein. A glutathione-S-transferase (GST)-Raf-1 construct (N-domain with residues of 1 to 149) was provided by Dr Mark Marshall (Indiana University, Indianapolis, Ind). For expression of the GST-Raf-1 fusion protein, an overnight culture was diluted (1:100) into fresh LB (Luria broth) medium containing ampicillin (100 µg/mL) and grown at 37°C to an OD₆₀₀ of 0.5. The culture was equilibrated to 30°C before 1-mmol/L isopropyl-β-D-thiogalacto-pyranoside (Sigma Co, St Louis, Mo) was added to induce GST-Raf-1 protein expression. After 3 hours of induction at 30°C, the cells were pelleted, resuspended in PBS buffer, and incubated overnight at -70°C. The lysate was sonicated, and the clear lysate was tumbled with glutathione-Sepharose beads (Pharmacia Biotech Inc, Piscataway, NJ) for 30 minutes. The beads were then washed 4 times with PBS buffer, and GST-Raf-1 protein was eluted with 10-mmol/L reduced glutathione (pH 8.0; Sigma Co). The GST-Raf-1 fusion protein was dialyzed against Tris-hydrochloric acid (HCl) buffer (pH 8.0) in aliquot, snap frozen, and stored at -70°C. The purity and concentration of this GST-Raf-1 protein was determined in a 12% SDS-polyacrylamide gel electrophoresis (PAGE) gel.

Gel Electrophoresis. Electrophoresis was performed in a vertical electrophoresis apparatus (Life Technologies Inc, Bethesda, Md) with 12% SDS-PAGE. The acrylamide concentrations of the running gel and the stacking gel were 12% and 5%, respec-

tively. The running gel (10 mL of 29% acrylamide and 1% bisacrylamide, 6.3 mL of Tris [pH 8.8], 0.25 mL of 10% SDS, and 8.2 mL of distilled water) was polymerized with 0.25 mL of ammonium persulfate and 10 µL of tetramethylethylenediamine (TEMED). After polymerization, a 5% stacking gel (1.7 mL of 29% acrylamide and 1% bisacrylamide, 1.25 mL of 1.0-mol/L Tris [pH 6.8], 0.1 mL of 10% SDS, 6.8 mL of distilled water, 0.1 mL of ammonium persulfate, and 10 µL of TEMED) was layered over the running gel. The polymerized gel was placed in the buffer-filled electrophoresis apparatus (250-mmol/L glycine [pH 8.3], 25-mmol/L Tris, and 0.1% SDS). The samples were mixed with the same volume of gel-loading buffer (100-mmol/L Tris chloride [pH 6.8], 4% SDS, 0.2% bromophenol blue, 20% glycerol, and 200-mmol/L dithiothreitol) and heated at 100°C for 3 minutes. Prestained high-molecular weight marker proteins (Life Technologies Inc) were used as molecular weight standards. The gel was run at 90 V for 7 hours. Separated proteins were then stained with Coomassie brilliant blue (Bio-Rad, Melville, NY) and destained with 45% methanol and 10% acetic acid in distilled water. The acrylamide, bisacrylamide, ammonium persulfate, and TEMED were purchased from Bio-Rad. The bromophenol blue, glycerol, and dithiothreitol were purchased from Sigma Co.

Transfer of Proteins to PVDF Membrane for Western Blot or Microsequence. For Western blot or microsequence, the SDS-PAGE gel, as described previously, was transferred immediately to a polyvinylidene difluoride (PVDF; Bio-Rad) membrane without gel staining in a semidry type transblot cell (Bio-Rad) with 10-mmol/L CAPS solution (3-[cyclohexylamino]-propanesulfonic acid, pH 11) for 1 hour. The protein-transferred PVDF membrane was dried on 3M paper until ready for Western blot or microsequencing. The gel, after protein transfer, was stained with Coomassie brilliant blue to visualize the efficiency of the transfer.

Western Blot. The protein-transferred PVDF membrane was washed 1 time with TTBS buffer (20-mmol/L Tris, pH 7.5, 500-mmol/L NaCl, and 0.025% Tween 20). Nonspecific staining was blocked by the addition of 25% normal goat serum in TTBS — containing 0.02% sodium azide for the patients' sera experiment, or 5% nonfat milk in 10-mmol/L Tris (pH 7.5), 100-mmol/L NaCl, and 0.1% Tween 20 for the Raf-1 monoclonal antibody experiment — at room temperature for 1 hour. The PVDF membrane was then incubated with patients' sera (1:50 dilution with TTBS containing 25% goat serum and 0.02% sodium azide) or Raf-1 (1:1,000 dilution) specific monoclonal antibodies (Transduction Lab, Lexington, Ky)

IDENTITY OF 28 KILODALTON PROTEIN

	40	50	Identity
28 kd protein	IVQQFGFQR	RASDDGKLTQ	
Human Raf-1	Y	D	89.5%
Chick Raf-1	Y	ISD	78.9%

Partial sequence of 28 kd protein (residues at 41 to 60) determined by microsequence showed 89.5% identity to human or rat Raf-1 protein and 78.9% to chick in search of Swiss Protein Database.

overnight at room temperature. This Raf-1 monoclonal antibody recognizes amino acids 162 to 378 of the human Raf-1 protein. The membrane was then washed 3 times with TTBS buffer and incubated with a peroxidase-conjugated goat anti-human polyvalent immunoglobulin (1:2,000 dilution, Accurate Chemical and Scientific Corp, Westbury, NY) for the patients' sera experiment, or peroxidase-conjugated anti-mouse IgG (1:2,000 dilution, Sigma Co) for the Raf-1 monoclonal antibody experiment, at room temperature for 2 hours. The PVDF membrane was washed 2 more times with TTBS at room temperature for 10 minutes. The staining color was developed by the addition of 0.05-mol/L Tris-HCl (pH 7.6) containing 0.02% 3,3'-diaminobenzidine (Chemicon International Inc, Temecula, Calif) and 0.01% hydrogen peroxide.

Microsequence. The 28 kd protein in the transferred PVDF membrane was carefully cut out for N-terminal sequencing by the method of classic automated Edman degradation (Applied Biosystem, Ragweed City, Calif). The Swiss Protein Database was used to match this protein sequence.

Determination of Raf-1 Antibodies From Meniere's Patients' Sera by ELISA. The Raf-1 specific antibodies from the sera of 27 patients with Meniere's disease were examined by an enzyme-linked immunosorbent assay (ELISA) as follows. Fifty microliters of recombinant GST-Raf-1 protein (5 µg/mL in 0.1-mol/L carbonate buffer, pH 9.6) was dispensed in each well of a polystyrene microtiter plate (Costar, Cambridge, Mass) and incubated overnight at 4°C. The plates were washed 5 times with 0.05% PBS-Tween buffer and incubated overnight with ε-chain specific anti-human IgG antibodies (Sigma Co) at 4°C. The plates were washed 5 times (0.05% PBS-Tween buffer) before the addition of a citric acid-phosphate buffer (pH 5.0) containing 0.15 mg/mL of *o*-phenylenediamine (Sigma Co). The color was developed at room temperature, and the reaction was stopped by 2.5-mol/L sulfuric acid. The color was measured at 492 nm (Bio-Rad).

RESULTS

Raf-1 Protein as Potential Autoantigen in Meniere's Disease. In this study, we were interested in

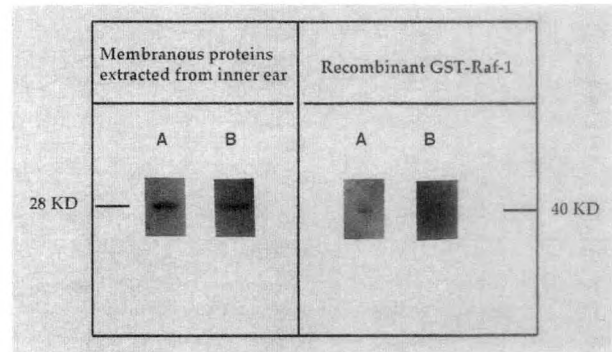


Fig 1. Twenty-eight kilodalton positive sera from patients with Meniere's disease reacted with 28 kd and recombinant glutathione-S-transferase (GST)-Raf-1 protein in Western blot analysis. Sera from 2 patients with Meniere's disease (patients A and B) reacted with 28 kd protein extracted from membranous part of inner ear of guinea pig as shown in left panel. Same sera also reacted with recombinant GST-Raf-1 protein (40 kd) as shown in right panel.

identifying the 28 kd inner ear membranous protein that reacts with the sera from patients with Meniere's disease. The 28 kd protein was purified through SDS-PAGE, transblotted to a PVDF membrane, and subjected to microsequencing. Nineteen amino acids (N'-IVQQFGFQRRASDDGKLTQ-C') were identified with an initial yield of approximately 78.6 pmol. When we attempted to match this sequence in the Swiss Protein Database, we found that this sequence is 89.5% homologous with human Raf-1 protein at residues 41 to 60, and 78.9% homologous with chick Raf-1 at residues 41 to 60 (see Table). The amino acid sequence of Raf-1 protein from the guinea pig is not available.

Sera From Patients With Meniere's Disease Reacted With 28 kd Protein and Raf-1 Protein. It was shown in a previous study that in Western blot analysis, 29% of patients with Meniere's disease had antibodies against the 28 kd protein extracted from the membranous part of the guinea pig inner ear.¹⁰ This 28 kd protein was identified as Raf-1 protein. In this study, we investigated whether sera from these 28 kd protein-positive patients with Meniere's disease had antibodies against the recombinant Raf-1 protein. A purified recombinant GST-Raf-1 protein was electrophoresed in a 12% SDS-PAGE gel and transblotted to a PVDF membrane for Western blot analysis. As shown in Fig 1, the sera from 2 patients had antibodies that recognized this recombinant GST-Raf-1 protein (amino acid residues 1 to 149) at a molecular weight of 40 kd. We also observed that sera from 16 of the 27 patients (59%; including 7 who showed positive reactivity with a 28 kd membranous extracted protein in Western blot analysis) recognized GST-Raf-1 protein in ELISA (Fig 2). In a separate experiment, sera from only 2 of 21 patients with

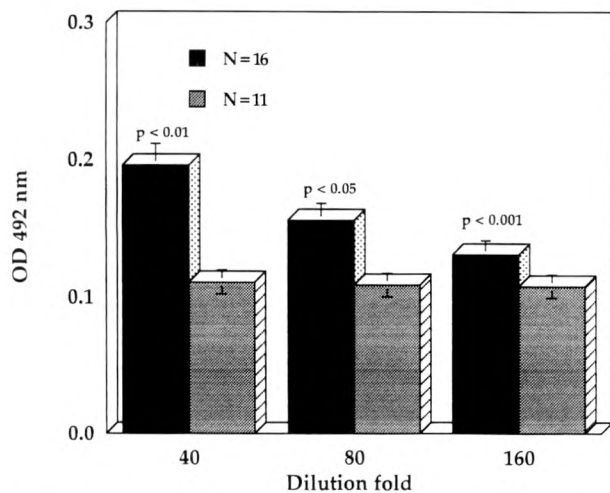


Fig 2. Summary of enzyme-linked immunosorbent assay (ELISA) results. Sixteen of 27 sera from Meniere's disease patients showed positive reactivity (from 1:40 to 1:160 dilution) with recombinant GST-Raf-1 protein in ELISA analysis, whereas 11 patients showed negative value. OD — optical density; p values are based on Student's *t*-tests.

IPBSNHL (10%) showed reactivity to recombinant GST-Raf-1 protein (data not shown).

Raf-1 Protein Is Present in Membranous Part of Inner Ear, But Not in Neural Part of Inner Ear, Facial Nerve, or Brain Tissue. Raf-1 protein is highly conserved among species and expressed in all cell types with a molecular weight of 74 kd. At present, it is not clear whether this 28 kd protein is a degraded form of Raf-1 protein. In this study, we examined whether this 28 kd protein can be recognized by a Raf-1 monoclonal antibody. The extracted proteins from the membranous fraction of the inner ear, neural part of the inner ear, facial nerve, and brain tissues were electrophoresed in a 12% SDS-PAGE gel and transblotted to a PVDF membrane for Western blot analysis. As shown in Fig 3, Raf-1 monoclonal antibodies recognized 115 kd and 74 kd extracted proteins from all types of tissue. The 74 kd protein is the Raf-1 protein. It is not clear whether the 115 kd protein represents a different form of Raf-1 protein, with sugar and lipid, or a completely different protein. However, Raf-1 monoclonal antibodies bound to a protein with a molecular weight of 28 kd from the membranous fraction of the inner ear, but not to those from other tissues such as the neural part of the inner ear, facial nerve, or brain.

DISCUSSION

We have reported that sera from 3 of 6 patients with Meniere's disease had antibodies against a 30 kd protein extracted from human retrocochlear tissue.⁴ The human whole cochlear tissues used in this study were obtained from living patients undergo-

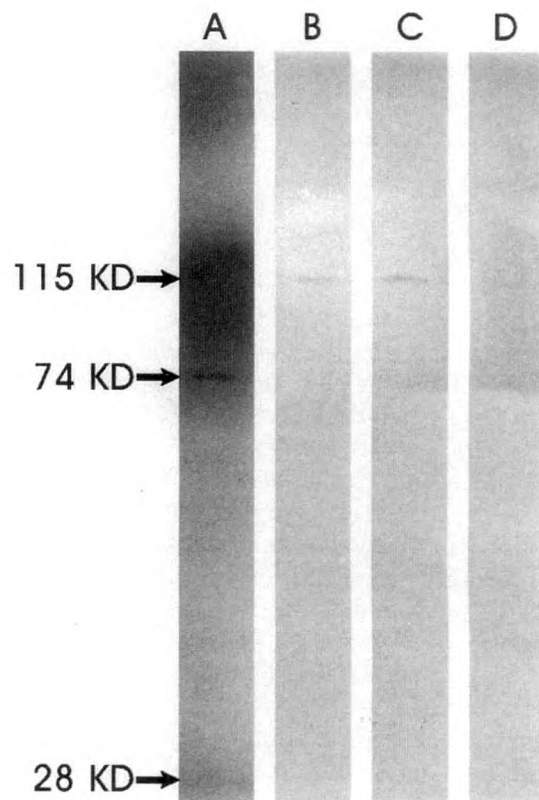


Fig 3. Raf-1 protein presented in membranous part of inner ear, but not in neural part of inner ear, facial nerve, or brain tissue. Raf-1 monoclonal antibody recognized 28 kd protein extracted from membranous part of inner ear of guinea pig. Raf-1 monoclonal antibody also reacted with 74 kd and 115 kd proteins extracted from tissues: membranous part (A) and neural part of inner ear (B), facial nerve (C), and brain tissue (D).

ing inner ear microsurgical dissection. Because the source of human inner ear tissue was extremely limited, we extended our study by using guinea pig inner ear tissue. By separating the inner ear tissue into its membranous and neural parts, we observed that 53% (24 of 45) of patients with various inner ear diseases had antibodies against inner ear proteins, compared with 0% of control subjects. Of the 10 proteins (ranging from 25 to 79 kd) that showed a positive reaction with patients' sera, the 28 kd protein was unique in that it was only observed in the membranous fraction of the inner ear, not in the neural part of the inner ear or other organs such as the brain or heart. Moreover, this 28 kd protein showed highly positive reactions with the sera of patients with Meniere's disease (7 of 25 patients, 28%) in Western blot analysis. We also observed that the sera from 2 of 33 patients with inner ear disease (6%) characterized by hearing loss and tinnitus had antibodies against a 30 kd protein from the membranous fraction of the inner ear.¹⁰ At present, it is not clear whether the 28 kd membranous protein from the inner ear of guinea pigs

corresponds to the 30 kd protein extracted from the cochlea tissue of humans.⁴

Cao et al⁶ have reported that sera from patients with various inner ear diseases had antibodies against a 30 kd protein extracted from the inner ear of guinea pigs. In that study, sera from 28% (12 of 43 patients) of patients with IPBSNHL, 46% (13 of 28 patients) with Meniere's disease, 40% (2 of 5 patients) with otosclerosis, and 17% (1 of 6 patients) with sudden deafness had antibodies that reacted with a 30 kd protein extracted from guinea pig inner ear tissue. It is of interest to note that sera from 4% (2 of 52 samples) of control subjects showed antibodies against this 30 kd protein. This 30 kd protein was not identified in any other tissues: brain, kidney, lung, or heart. Localization of this protein indicated that this 30 kd protein is extremely abundant in the modiolus pool and Corti's organ, but not in the spiral ligament or stria vascularis of the inner ear. Therefore, it is suspected that this 30 kd protein is associated with the acoustic nerve.⁸ Further characterization of this 30 kd protein showed that it was the major peripheral myelin protein: PO protein.⁹ PO protein is highly conserved in humans, rats, mice, and cows. It is of interest to note that both the 28 kd and 30 kd PO proteins were extracted from the inner ear of guinea pigs.⁸⁻¹⁰

We have purified and microsequenced this 28 kd protein, and the protein sequence was homologous to that of the Raf-1 protein. These results clearly suggest that the 28 kd and 30 kd proteins are entirely different proteins. The sera from 2 patients with Meniere's disease and antibodies against 28 kd protein indeed reacted with recombinant GST-Raf-1 protein in the Western blot analysis (Fig 1). On ELISA, 16 of the 27 patients with Meniere's disease (59%) had antibodies against recombinant GST-Raf-1 protein (Fig 2). However, only 2 of 26 patients with IPBSNHL showed positive reactivity to recombinant GST-Raf-1 protein (data not shown). These results suggest that Raf-1 antibodies have a much higher rate of expression in patients with Meniere's disease than in those with IPBSNHL. The discrepancy between observations of Raf-1-positive sera in patients with Meniere's disease in this study (15 of 27; 56%) and previous observations of 28 kd protein (7 of 25; 28%) is probably due to the methods (Western blot analysis versus ELISA) and antigens (membrane-extracted protein from guinea pigs versus recombinant GST-Raf-1 protein) applied in these 2 studies. This 28 kd protein is also recognized by Raf-1 monoclonal antibodies and is present only in the membranous part of the inner ear, not in the neural part of the inner ear, facial nerve, or brain tissue (Fig 2). It is not clear whether this 28 kd protein is a degraded form of Raf-1 protein, which has a molecular weight of 74 kd.

Other tissues prepared under the same conditions did not contain the 28 kd protein; therefore, it is unlikely that this degradation is due to the protein extraction process. It is also possible that the 28 kd protein is a new protein that is highly similar to Raf-1 protein.

The Raf-1 protein belongs to the Raf protein family. Three members have been described: Raf-1, A-Raf, and B-Raf. Raf proteins are serine-threonine-specific protein kinases that conduct a signal transduction between the cell membrane and the nucleus. Raf proteins, like oncogenes, are highly conserved in mouse, rat, chicken, *Xenopus laevis*, *Drosophila melanogaster*, and *Caenorhabditis elegans*.^{12,13} Based on the homology among the Raf proteins, 3 conserved regions (CR) have been proposed. The CR1 and CR2 at the N-terminal site are considered to be critical for the regulation of Raf-1 activity. The mutation of these regions activates the oncogenic potential of Raf-1.¹⁴⁻¹⁶ The CR3 contains the protein kinase domain, and the C-terminal site is considered the catalytic domain. Raf-1 is a non-tissue-specific protein and plays a key role in a kinase cascade that regulates cell proliferation, differentiation, and development.¹⁷⁻¹⁹ Mitogen activates Raf-1 through phosphorylation; then, phosphorylated Raf-1 activates protein kinase (MEK). This phosphorylated MEK activates mitogen activating protein (MAP) kinase and leads to gene expression and DNA synthesis.¹⁹

Harris and Sharp²⁰ have shown that 35% of sera from patients with IPBSNHL reacted with a 68 kd protein extracted from bovine inner ear tissue. This 68 kd protein was later identified as a 70 kd heat shock protein (hsp70).^{20,21} It is of interest to note that other autoimmune diseases, such as Lyme disease and ulcerative colitis, have been reported to be associated with hsp70.²²⁻²⁴ In our previous study, we also observed that the sera from the patients with inner ear disease had antibodies that reacted with 25 kd, 46 kd, 52 kd, 67 kd, and 79 kd proteins.¹⁰ The results in that study suggest that 52 kd and 67 kd proteins are not tissue-specific proteins. It is not clear whether the 67 kd protein corresponds to hsp70.

Our observations and those of other laboratories suggest that multiple antigens are involved in the immunopathology of autoimmune inner ear diseases. All 3 of the study proteins (hsp70, myelin PO, and Raf-1 proteins) are non-tissue-specific proteins, and therefore nonspecific to inner ear tissue. It is of interest to investigate how these non-tissue-specific proteins are involved in autoimmune inner ear diseases. Several questions need to be addressed. If the 28 kd protein is a degraded Raf-1 protein, what is the biological function of the 28 kd protein? Why is

the 28 kd protein observed only in the membranous part of the inner ear tissue, given that Raf-1 is a non-tissue-specific protein? How does the immune mechanism target the 28 kd protein? Does the mutation

of this protein break down tolerance, or does the immune response to a virus induce a loss of tolerance to this protein? Clearly, more experiments are required to answer these questions.

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CLINICAL EXPERIENCE WITH BETA-TRACE PROTEIN AS A MARKER FOR CEREBROSPINAL FLUID

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β -Trace protein is an immunological marker for the detection of cerebrospinal fluid traces. The aim of the study was to evaluate the predictive value of the β -trace protein test. We investigated 145 specimens for cerebrospinal fluid using β -trace protein. All case notes were retrospectively reviewed and tabulated for indication and procedure with focus on outcome. The specimens were analyzed by immunoelectrophoresis. β -Trace protein was detected in 62 specimens and was absent in 83. In correlation with the clinical course, the clinical findings, the results of high-resolution computed tomography of the paranasal sinuses or petrous bone, computed tomographic cisternography, magnetic resonance imaging, indium 111-pentetic acid radionuclide cisternography, intraoperative findings, and visualization using sodium-fluorescein, there were no false-positive results. In 6 cases, a false-negative result occurred. The overall accuracy was 95.68%. The β -trace test has a specificity of near 100% and a sensitivity of 91.17%. Analysis of β -trace protein is a valuable test and has some advantages in comparison with the β 2-transferrin assay.

KEY WORDS — beta-trace protein, cerebrospinal fluid, prostaglandin D synthase.

INTRODUCTION

In skull base surgery, methods for the detection of cerebrospinal fluid (CSF) leaks are very important. The cause of CSF rhinorrhea or otorrhea may be either traumatic or nontraumatic. Nontraumatic causes include inflammatory processes and tumors. The term "spontaneous" CSF leak is controversial and should be replaced by "idiopathic" CSF rhinorrhea or otorrhea.¹ In search of a CSF fistula, many different tests are performed, such as Queckenstedt's maneuver, testing for glucose, high-resolution computed tomography (HRCT), magnetic resonance imaging, computed tomographic cisternography, and indium 111-pentetic acid (¹¹¹In-DTPA) radionuclide cisternography. Often, it is difficult not only to confirm a CSF leak, but also to localize exactly the site of the lesion. Therefore, it is helpful first to apply an immunologic method for the detection of CSF, and second, to visualize the CSF. The CSF can be visualized with intrathecal sodium fluorescein and endoscopic blue light.

β -Trace protein is a durable protein with a molecular weight of approximately 26,000 d. After the prostaglandin D synthase (PGD-S) [PGS-S, prostaglandin-H₂ D-isomerase, (5Z,13E)-(15S)-9a, 11-epoxydioxid-15-hydroxyprosta-5, 13-dienoate D-isomerase, EC 53992] gene was cloned, it became apparent that PGD-S and β -trace protein are identical.² This enzyme is a member of the lipocalin family of secretory proteins that transport small lipophilic substances. After albumin, β -trace protein is the second

most abundant protein in human CSF. It has been detected in CSF, human perilymph,³ rat retina cells,⁴ seminal fluid, and urine.⁵ The highest concentrations were found in human perilymph,³ CSF, and seminal fluid.⁶ The synthesis and function of β -trace protein are not fully clarified, but it seems to play an important role in regulating the sleep and waking states.⁷ β -Trace protein is stable for several days, even at room temperature.

The β -trace protein assay was introduced in 1987 by Felgenhauer et al⁵ as an immunologic method. By rocket immunoelectrophoresis (Laurell's electroimmunoassay), the sample fluid precipitates with a monospecific polyclonal antibody. Laurell's rocket electrophoresis is a 1-dimensional electrophoretic method that can be performed within 3 hours. The level of β -trace protein in serum is so low that it is not detectable by rocket immunoelectrophoresis. The detection limit of the protein itself is 2 mg/L. The detection limit of CSF when β -trace protein is used is 60 mL/L, accordingly. Sample volumes of 5 μ L containing less than 10% CSF are sufficient.⁵

The sensitivity and specificity of the β -trace test have not been published, and the aim of this study was to evaluate the predictive values of the β -trace assay for the detection of CSF traces.

METHODS

Between 1982 and 1999, 145 specimens from 98

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TABLE 1. ANATOMIC SITES FROM WHICH SAMPLES WERE TAKEN

	β -Trace-Positive			
	No.	%	No.	%
Anterior cranial fossa				
Orbital cavity	0	0	0	0
Frontal sinus	5	3.45	2	1.37
Ethmoid cells	35	24.14	10	6.89
Sphenoid sinus	5	3.45	4	2.76
Maxillary sinus	3	2.07	1	0.68
Nasal cavity and cribriform lamina	45	31.03	21	14.48
Middle cranial fossa				
Petrous bone and outer ear canal	52	35.86	24	16.55
Posterior cranial fossa	0	0	0	0

patients were investigated for β -trace protein. The average age of the patients was 46.5 years, with a range of 3 to 82 years.

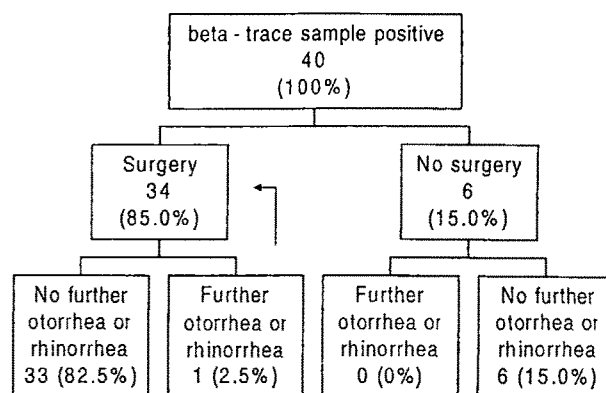
Specimens containing a minimum of 10 μ L were investigated by Laurell's rocket immunoelectrophoresis. The standard electroimmunoassay as described elsewhere⁵ was performed with a gel composition of 1.5% agarose (Merck, Darmstadt, Germany), 0.02-mol/L barbital buffer, pH 8.6, 1% antiserum, 1% polyethylene glycol 6000 (Merck), an electrophoresis buffer of 0.02-mol/L barbital buffer, pH 8.6, and a monospecific polyclonal antibody that was produced in rabbits. Electrophoresis was performed for 3 hours at 18°C at a constant voltage of 250 V.

As we had no alternative immunologic test available for the proof of CSF traces, the clinical course and relevant investigations were used to evaluate the predictive value of the β -trace test. All case notes were reviewed retrospectively. The results of HRCT of the temporal bone and the paranasal sinuses in the axial and coronal planes, MRI, CT cisternography, ¹¹¹In-DTPA radionuclide cisternography, and intraopera-

TABLE 2. INVESTIGATIONS AND INTRAOPERATIVE FINDINGS, INCLUDING COMBINED OR REPEATED TESTS

Investigations	No.	Signs of CSF Leakage	
		No.	%
Intraoperative and endoscopic findings	108	54	50.0
High-resolution computed tomography	72	9	12.5
Magnetic resonance imaging	12	0	0
Computed tomographic cisternography	6	2	33.3
Sodium fluorescein visualization	5	2	40
Indium 111-pentetic acid radionuclide cisternography	4	2	50
Glucose test	1	1	

CSF — cerebrospinal fluid.

Fig 1. Clinical course of cases with positive β -trace result.

tive CSF visualization with sodium fluorescein were reviewed. "No evidence of CSF" was noted when the clinical course, the intraoperative findings, and an additional investigation gave no evidence of a CSF leak. "Evidence of CSF" was noted when the clinical course, intraoperative findings, or an additional investigation gave a direct or indirect sign of CSF or CSF leakage.

RESULTS

The majority (64.14%) of the specimens were taken from the nose or from the anterior cranial fossa; 35.86% were collected from the petrous bone or from the outer ear canal (Table 1). Among all 98 patients, there was none with severe renal disease.

The underlying disease was inflammation (38.77%), head trauma (24.49%), malignant disease (29.59%), or unknown (8.16%).

"Additional investigations" were performed not only to establish the diagnosis of a CSF leak, but also to identify the exact location of the lesion. In Table 2, all additional investigations are itemized. The most frequent radiologic investigations were HRCT of the paranasal sinuses in the axial and coronal planes and HRCT of the temporal bone. Only in selected cases was MRI, CT cisternography, intraoperative CSF visualization with sodium fluorescein, or ¹¹¹In-DTPA radionuclide cisternography performed. Intraoperative and endoscopic findings gave evidence of a CSF fistula in 50% of specimens. Testing for glucose was performed only once, because it is an unreliable marker for CSF.

All 40 patients with a positive β -trace test either underwent surgery or were observed for at least 1 week as inpatients (Fig 1). In 34 cases, a CSF leak was found intraoperatively. There was no further, postoperative CSF flow in 33 of these cases. In 1 case, a CSF leak recurred and a revision operation was needed. Six patients with a positive test were not operated on after sampling for β -trace protein.

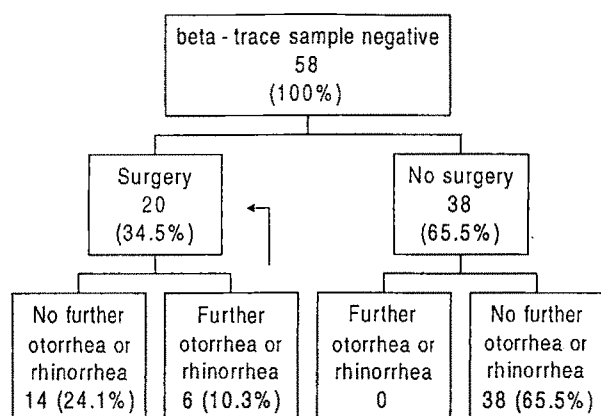


Fig 2. Clinical course of cases with negative β -trace result.

These included 3 patients who had an operation for acoustic neuroma by a translabyrinthine or transtemporal approach followed by wound discharge. One patient had wound discharge after surgery for a jugular glomus tumor, and 1 patient presented with a temporal bone fracture and otorrhea. They received intravenous antibiotics and, under close observation, did not show any signs of meningitis; their CSF discharge ceased spontaneously within a few days. One patient with postmeningitis rhinorrhea refused surgical revision. In 5 cases, the CSF flow persisted and a revision operation was needed.

Of the 58 patients with a negative β -trace result, 38 were not operated on immediately, and there was a lack of evidence of a CSF flow, which was confirmed by subsequent management (Fig 2). These were patients with vasomotor rhinitis (4.3%), chronic sinusitis (30.4%), chronic otitis media (17.4%), a history of a head trauma (34.8%), or malignant disease (13.0%). In 20 cases, it was necessary to perform surgery because of developing meningitis, chronic sinusitis with polyposis, or malignancy. In spite of the β -trace result, 5 patients showed a CSF leak intraoperatively; their β -trace results (6 samples) were false-negative as mentioned above. In 1 of them, pure thick pus was taken, which was nearly impossible to separate by immunoelectrophoresis, and in another case, the sample volume was less than 5 μ L.

The average follow-up, usually performed on an outpatient basis, was 15.39 weeks.

All positive results were confirmed either by the clinical course or by additional findings, and we could only estimate the specificity to be near 100%. The sensitivity was calculated at 91.17%, and the overall accuracy was 95.68% (Table 3).

DISCUSSION

As the average annual risk of developing meninge-

TABLE 3. TWO-BY-TWO CONTINGENCY TABLE OF BETA-TRACE RESULTS

	Evidence of CSF	No Evidence of CSF	Total
β -Trace-positive	62	0	62
β -Trace-negative	6	77	83
Total	68	77	145

No evidence of CSF was defined as situation in which clinical course, intraoperative findings, and additional investigation gave no direct or indirect sign of CSF leak. Evidence of CSF was defined as situation in which clinical course, intraoperative findings, and/or additional investigation gave direct or indirect sign of CSF or CSF leakage. Sensitivity is 91.17%, specificity is near 100%, and overall accuracy is 95.68%.

tis from a CSF leak at the anterior skull base is 9.8%, CSF fistulas are still a challenging task.⁸ A reliable diagnostic tool for the proof of suspected CSF traces is very important in skull base surgery. Ideally, the method should be noninvasive, without any radiation, easy to perform, and able to be performed with small quantities of sample. Only the β 2-transferrin test and the β -trace test meet these requirements.

Oberascher and Arrer⁹ developed the β 2-transferrin assay. This method takes at least 5 hours to perform in the laboratory. The β 2-transferrin assay is performed by 2-dimensional immunoelectrophoresis or by immunofixation. Body fluids with a protein content of 5 g/L or higher, often found in specimens taken from the nose, have to be precipitated with ammonium sulfate before β 2-transferrin immunoelectrophoresis. Furthermore, contamination with blood requires column chromatography in order to eliminate hemoglobin. Therefore, it requires more time (5 to 8 hours) to perform the β 2-transferrin assay in the laboratory.⁹ β 2-Transferrin is absent from serum and has been identified so far in CSF, perilymph, and aqueous humor. In subjects with cirrhosis or genetic protein variants, however, β 2-transferrin has been detected in serum.⁸ Simmen et al¹⁰ found that the β 2-transferrin determination has a sensitivity of 79%, whereas Skedros et al¹¹ described a sensitivity of near 100% and a specificity of about 95% (n = 88) for the β 2-transferrin test.

In comparison to the β 2-transferrin test, the β -trace assay has some advantages. As the β -trace test is a 1-dimensional electrophoresis, it can be done within 3 hours. The β -trace test has the limitation that the protein is also contained in urine. In cases of acute glomerulonephritis or terminal renal insufficiency, the β -trace protein concentration is increased in serum. Therefore, patients with renal filtration barrier disorders should not be submitted to CSF detection by β -trace protein.

A new immunofluorometric assay (IMFA) based on enzymatic amplified time-resolved fluorometry

has been established.¹² β -Trace protein can be measured by this IMFA, and the detection limit is 0.05 μ g/L. This IMFA is about 1,000-fold more sensitive than immunoelectrophoresis and can be performed within 15 minutes.

A valuable diagnostic tool is available to the skull base surgeon with the β -trace test. The method is noninvasive and easy to perform. As the protein is durable, the specimens can be sent by mail. Clinical experience has revealed that the smallest traces of CSF can be detected by β -trace protein. The test, us-

ing rocket electrophoresis, is extremely specific (near 100%) and very sensitive (91.17%).

As bony lesions and their location are always of great interest, HRCT was mainly performed. Invasive procedures were necessary in selected cases. In comparison to the β 2-transferrin test, the β -trace test is faster and offers a higher specificity.

We believe that the β -trace test is a valuable tool for the skull base surgeon, neurosurgeon, ophthalmologist, maxillofacial surgeon, otorhinolaryngologist, or head and neck surgeon.

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UNIQUE CASE OF PULSATILE TINNITUS

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Tinnitus is a common symptom encountered by otolaryngologists. Pulsatile tinnitus is rare and can present a diagnostic challenge. Establishing a diagnosis is important, because pulsatile tinnitus may indicate serious intracranial or extracranial disease. A unique case of pulsatile tinnitus caused by cervical artery dissection is presented, along with the differential diagnosis and treatment.

KEY WORDS — cervical artery dissection, pulsatile tinnitus.

INTRODUCTION

Although tinnitus is a common symptom encountered by otolaryngologists, pulsatile tinnitus is rare and can present a diagnostic challenge. Timely diagnosis is important, because the underlying etiologic mechanism may be serious intracranial or extracranial disease. The purpose of this report is to present a unique case of pulsatile tinnitus caused by bilateral carotid artery and unilateral vertebral artery dissection.

The arterial origins of pulsatile tinnitus are numerous. The sensation of pulsatile tinnitus can result from an aberrant vessel location, increased flow, or turbulent flow within a vessel lumen. Tinnitus that results from an aberrant vessel location may be due to an ectopic intratympanic internal carotid artery (ICA),¹ a persistent stapedial artery,² or an aberrant vessel in the stria vascularis.³ Increased arterial flow within the temporal bone and the perception of tinnitus can arise from arteriovenous malformations⁴ and Paget's disease.⁵ Turbulent flow within the carotid artery due to atherosclerotic plaques has recently received attention as a common cause of pulsatile tinnitus. Neck bruits generated by turbulent flow at the atherosclerotic-stenotic segment are transmitted to the skull base and cochlea and perceived as tinnitus.⁶ In a similar manner, cervical artery dissections can also cause luminal narrowing, turbulent flow, and resulting pulsatile tinnitus.

Cervical artery dissections are divided into those that occur spontaneously and those that are the result of trauma. The presentations of these two types of dissections are not identical. Dissections that are not obviously caused by vascular disease or major blunt trauma are considered spontaneous. Patients with

spontaneous carotid artery dissection usually present mild cerebral ischemic symptoms such as transient ischemic attacks.⁷ Only 5% of patients with spontaneous carotid artery dissection progress to massive cerebral infarction.⁸ Additional symptoms include acute unilateral headaches and neck pain with ipsilateral Horner's syndrome.⁷ Pulsatile tinnitus is the sole presenting symptom in 4% of cases involving spontaneous extracranial carotid artery dissections, and it is an associated symptom in 35%.⁷ Tinnitus caused by vertebral artery dissection is unusual in the absence of other neurologic symptoms.⁹

On the other hand, cervical artery dissections due to blunt trauma, unlike those of a spontaneous nature, have not, to our knowledge, been reported to cause pulsatile tinnitus as the sole presenting complaint. We present a unique case of pulsatile tinnitus due to bilateral carotid artery and unilateral vertebral artery dissection that followed a major blunt trauma.

CASE REPORT

A 32-year-old woman driving a car was involved in a head-on motor vehicle accident in December 1993. She was wearing a combination shoulder-lap belt at the time of the accident. She had no loss of consciousness, head injury, or external signs of trauma other than a fractured clavicle. Three days after the accident, she noted a right-sided aural pressure and pulsatile tinnitus. There was no associated otorrhea, otalgia, hearing loss, headache, or visual changes.

The patient presented to our otolaryngology clinic 2 weeks after the accident for an evaluation of her pulsatile tinnitus. On examination, both tympanic membranes and external auditory canals were nor-

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Fig 1. Magnetic resonance angiogram of right internal carotid artery (ICA). Arrow points to narrowing of lumen of right ICA.

mal. A tuning fork examination showed a midline Weber test result and a Rinne test with greater air conduction than bone conduction bilaterally. There were no external signs of trauma; however, a bruit was noted over the right side of the neck. An audiogram revealed normal hearing and normal speech reception threshold and discrimination scores.

Because of the high suspicion for possible vascular injury, the patient was sent for magnetic resonance imaging (MRI). The scan demonstrated bilateral ICA dissections and a right vertebral artery dissection. The dissections began just above the carotid bulbs and continued to the base of the skull. The right ICA had a residual lumen of 10% (arrow in Fig 1), the left ICA had a residual lumen of 50% (B in Fig 2), and the right vertebral artery demonstrated abnormal flow over a 3-cm region (A in Fig 2). An MRI scan of the brain showed no evidence of infarction. A carotid ultrasound scan confirmed that the arteries were patent despite the severe narrowing.

After the severity of her injuries was discovered, the patient was admitted for anticoagulation therapy with intravenous heparin. She was then converted gradually to oral warfarin anticoagulation over the next several days. During her hospital stay, the patient suffered no neurologic sequelae.

Follow-up duplex ultrasound examination of the

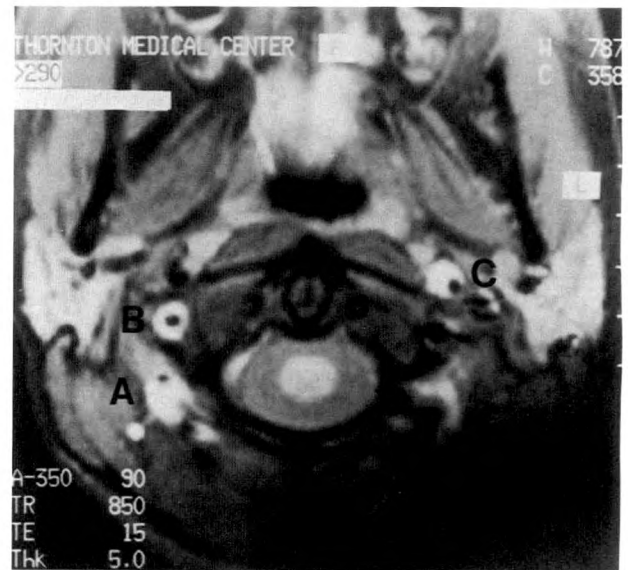


Fig 2. Demonstration of intraluminal narrowing and hyperintense signal within lumen by fat-suppression T1-weighted magnetic resonance imaging. A — right vertebral artery; B — right ICA; C — left ICA.

carotid arteries and the vertebral artery on an outpatient basis at 6 and 12 months demonstrated normal extracranial cervical arteries. The patient remains asymptomatic.

DISCUSSION

The incidence of carotid artery dissection after major blunt trauma is rare, with a reported incidence of 0.08%. The risk of carotid artery dissection is increased when there are concurrent head, facial, and cervical injuries.¹⁰ Motor vehicle accidents are responsible for as many as two thirds of cases.¹¹ Additional causative injuries include interpersonal altercations, hanging, direct blows to the neck, chiropractic manipulation, and sporting accidents. Minor trauma such as coughing,¹² nose blowing,¹³ and brushing teeth¹⁴ are additional causes for carotid artery dissection. Bilateral dissection is even more infrequent than unilateral dissection, with only 17 other cases reported.¹⁵

External signs of trauma are present in less than half of cases.¹⁶ The most common presentations of traumatic carotid artery dissections are symptoms due to compromise of cerebral perfusion. These include hemiparesis, alteration in the level of consciousness, aphasia, hemianopsia, and convulsions. The majority of patients become symptomatic within a few hours to days after the traumatic event.¹⁷ Rarely, symptoms may be delayed from months to as long as 10 years after the injury.¹⁸ Patients with a delayed discovery of carotid artery dissection usually present with symptoms of cerebral ischemia.¹⁹

One proposed mechanism of injury is hyperexten-

sion of the neck, which may compress the ICA against the transverse processes of C2 and C3.²⁰ Neck flexion with compression of the ICA between the angle of the mandible and the transverse processes of the upper cervical vertebrae has also been proposed. Other possible mechanisms of injury include damage due to a long styloid process,²¹ mandible fracture,²² intraoral trauma,²³ and traction of the hypoglossal nerve against the carotid artery.²⁴ Shoulder-lap belts that cause direct contusion to the carotid artery can also cause carotid dissection.²⁵ This may have been the mechanism of injury in our patient.

The incidence of vertebral artery dissection due to blunt trauma has been reported to be 0.2%,²⁶ with the majority of cases occurring from penetrating trauma.^{27,28} The most common presenting symptom of vertebral artery dissection is pain. This usually takes the form of a posterior occipital headache or neck pain ipsilateral to the side of the dissection. The pain precedes the onset of brain stem infarction by several hours to several weeks. The neurologic symptoms include nonspecific cerebellar and brain stem ischemic manifestations such as vertigo, dizziness, and hemisensory and motor symptoms.^{11,29} Wallenberg's syndrome has been reported to develop in as many as one third of patients and consists of ipsilateral palatal paresis, true vocal cord weakness, Horner's syndrome, and a crossed sensory deficit.

Vertebral artery dissections occurring as a result of abrupt changes in head position can be explained on an anatomic basis.³⁰ For most of its course, the vertebral artery is protected, surrounded by the transverse processes or the upper 6 cervical vertebrae. The artery is most susceptible to injury in its mobile distal portion as it leaves its bony canal at the level of the atlantoaxial joint.

Early diagnosis is essential if strokes resulting from either thrombotic emboli or insufficient flow are to be prevented by surgery or anticoagulation treatment. Historically, diagnosis of carotid artery and vertebral artery dissection had to be confirmed with angiography, an invasive method with its attendant risks. Furthermore, angiographic features of dissection are variable, except for the finding of a double lumen or an intimal flap. Currently, MRI and ultrasound examination allow early definitive diagnosis in most cases. The combined Doppler and duplex examination is sufficiently sensitive to detect occlusion (100% sensitivity) and moderate or high-grade stenosis (95.7% sensitivity). Low-grade stenoses can

escape diagnosis, but they are rare and present a low risk for embolic complications. Duplex examination will not detect retromandibular (high cervical) stenosis.³¹

Magnetic resonance imaging, including magnetic resonance angiography (MRA), may prove to be a sensitive noninvasive method for identification of carotid or vertebral artery aneurysms. Criteria for dissection seen on MRI are an increase in the external diameter of the artery, narrowing of the lumen, and a hyperintense signal within the arterial wall (Fig 2).³² The routine use of MRI as a technique for the diagnosis of cervical artery dissections is limited because of the inability of MRI to demonstrate direct signs of the patency of vessels and arterial flow. The sensitivity of MRI in detecting vertebral artery dissection has been reported to be 60%, with a specificity of 98%.³² The detection of carotid artery dissection is better, with a sensitivity of 84% and a specificity of 99%.³² However, as many as 20% of small intraluminal hematomas may be missed if large interslice gaps or thick slices are used.³³ The sensitivity of MRA for diagnosing vertebral artery disease is 97%, and the specificity is 98.9%.³⁴ The detection of carotid intraluminal abnormalities by MRA has a sensitivity of 95% and a specificity of 99%.³²

The treatment of carotid and vertebral artery dissections after blunt trauma remains controversial. In dissections of the ICA, stroke usually occurs in the first few days, necessitating early treatment.³⁵ Although there is no prospective randomized study available that proves the benefits of anticoagulation therapy in asymptomatic patients, many authors recommend early treatment with heparin followed by treatment with warfarin.^{36,37} Surgical treatment is reserved for patients with recurrent symptoms of cerebral ischemia despite anticoagulation therapy and is performed in the hope of preventing irreversible neurologic or retinal damage.³⁷

Cervical artery dissection, as shown in our case, represents a serious sequela of blunt trauma from the passive restraint of shoulder-lap belts. If one does not have a high index of suspicion, it can be missed. Although the majority of patients present with neurologic symptoms, subtle symptoms such as pulsatile tinnitus may aid in early recognition and treatment. Early recognition may prevent the undesirable sequelae of compromised cerebral perfusion. With sensitive, noninvasive testing, these more subtle symptoms can be explored more aggressively.

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WORD DEAFNESS AFTER RESECTION OF A PINEAL BODY TUMOR IN THE PRESENCE OF NORMAL WAVE LATENCIES OF THE AUDITORY BRAIN STEM RESPONSE

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We studied the case of a 48-year-old woman who had resection of a pineal body tumor in terms of postoperative audiological function. Postoperative magnetic resonance imaging disclosed partial inferior colliculi destruction and medial geniculate body degeneration. A pure tone audiogram revealed only moderate sensorineural hearing loss, but her speech perception was totally impaired. The binaural sound localization function was also impaired. The auditory brain stem response (ABR) showed waves I, III, and V to have normal latencies. The amplitude of wave III was larger than that of wave V. These results support the view that the waves of the ABR are elicited from multiple sources in the auditory brain stem nuclei and tracts. This case suggests a substantial role for the inferior colliculus and medial geniculate body in the processing of speech perception and sound localization.

KEY WORDS — auditory brain stem response, hearing loss, inferior colliculus, medial geniculate body, speech perception.

INTRODUCTION

It is well known that lesions in the central nervous system occasionally cause hearing impairment. Recent developments in radiologic examination, such as magnetic resonance imaging (MRI), have made it relatively easier to characterize the localization and the nature of the disorders. However, the mechanisms of verbal sound discrimination are poorly understood, partly because upper brain stem disorders are not as common as lower brain stem disorders.

Herein, we describe a patient in whom resection of a pineal body tumor led to hearing loss caused by inferior colliculus and medial geniculate body (MGB) damage, while preserving wave V of the auditory brain stem response (ABR).

CASE REPORT

Clinical History and Surgical Findings. The patient was a 48-year-old right-handed woman whose native language was Portuguese. She had moved to Japan 8 years before the onset of disease and spoke Japanese well. She had no hearing loss before surgery. She developed headaches and visual disturbances in the spring of 1996, and was found to have a pineal body tumor. In June 1996, she underwent surgery at the Department of Neurosurgery, Mie University School of Medicine. Although the tumor resection was accompanied by injury of the inferior

colliculus, the cerebral cortex and subcortex were not injured. A histologic examination revealed an astrocytoma. Immediately after the surgery, she noted bilateral hearing loss and was referred to the outpatient clinic of the Department of Otorhinolaryngology, Mie University School of Medicine. She had bilateral tinnitus without dizziness or vertigo. She showed no other neurologic abnormalities such as mental status change, agnosia, or apraxia, but had a mild visual disturbance when looking upward.

Communication. After the hearing loss, the patient could not understand verbal communications in either Japanese or Portuguese, whether presented as monosyllables, words, or sentences. She could speak, read, and write in both languages without difficulty and with the same competence as before the surgery. She could identify some nonverbal sounds, such as the ring of a telephone and a baby's cry. Further, she was able to distinguish some new sounds during the first year after the surgery. She also correctly identified pieces of music familiar to her before the surgery, but she could not understand the lyrics.

Magnetic Resonance Imaging. A postoperative MRI scan disclosed remaining tumor that was compressing and partially destroying the region, including the bilateral inferior colliculi and the MGB (Fig 1). The destruction of the inferior colliculi was more severe on the left side than on the right. The cerebral

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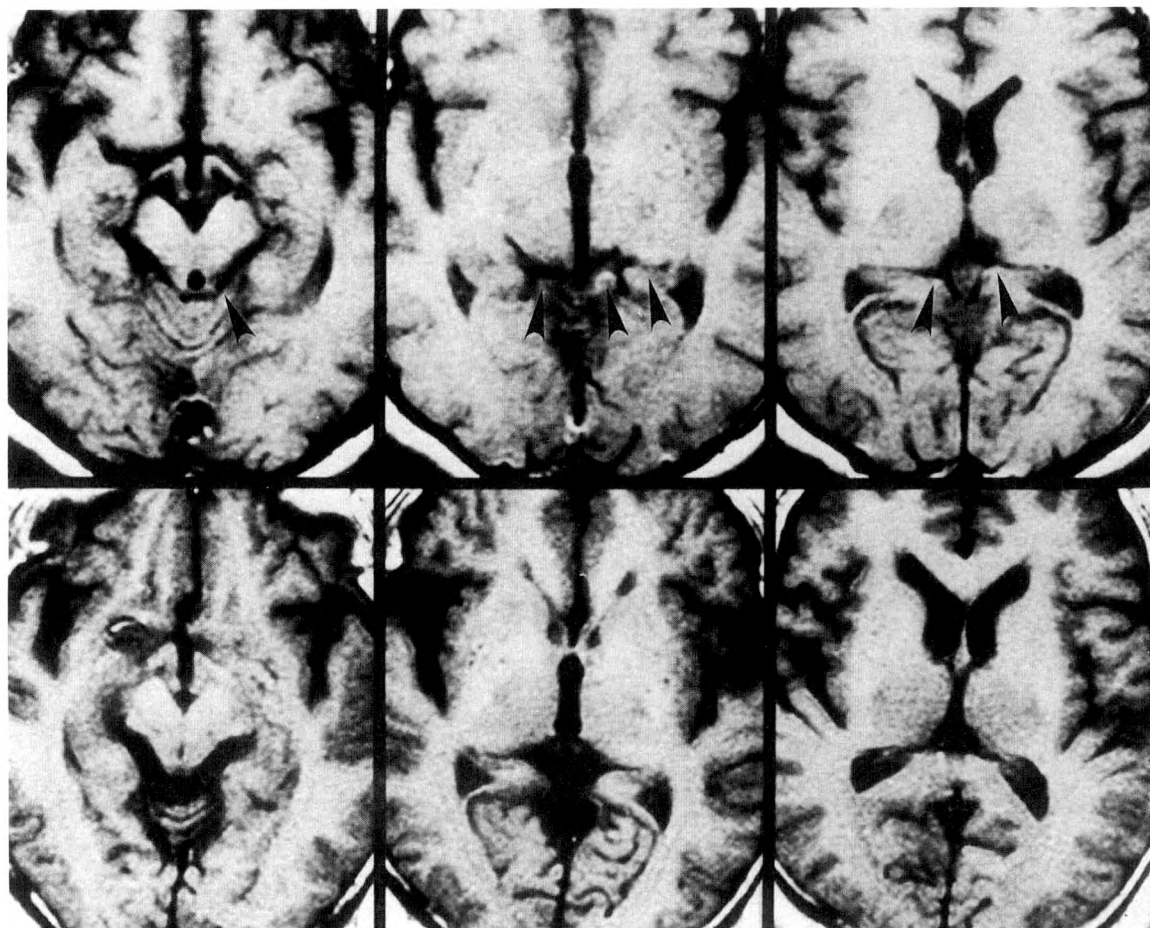


Fig 1. Axial T1-weighted magnetic resonance images of patient at 7 months after surgery (top) and of normal volunteer (age 60 years, male; bottom). Images of patient disclosed compressed and partially destroyed region including bilateral inferior colliculi and medial geniculate body (arrowheads). Cerebral cortex and subcortex appeared normal.

cortex and subcortex appeared normal.

METHOD

All audiological testing was done with the patient seated in a sound-treated room. Pure tone stimuli were generated via a conventional diagnostic audiometer (AA-70, RION, Japan), and speech stimuli were played on a cassette tape deck (V-45X TEAC, Japan), fed through the speech circuit of the audiometer, and transmitted through a headphone (AD-02, RION). The acoustic reflex threshold and decay were examined with an acoustic impedance meter (TA-2C, RION). The stimuli were transmitted from a headphone (AD-66, RION). A 220-Hz probe tone was transmitted from the probe (ET-02, RION). The function of binaural sound localization was examined with a warble tone generated via the audiometer. The warble tones were presented at random from one of the loudspeakers (FB-10A, RION) arranged at the patient's right and left sides.

An ABR study was conducted in a sound-treated room. A scalp electrode was attached high on the

forehead, and other electrodes to each earlobe, which served as the reference and ground. The impedance across the electrodes was maintained at less than 5 k Ω . The stimulus was a click generated from a 100- μ s rectangular electrical wave delivered to a TDH-39P headphone. The final waveforms were derived from 2,048 clicks. To obtain the waveform, averaging of the ongoing neuroelectrical activity was performed by Navigator version 4.18 (Biologic System Corp, Mundelein, Ill) with bandpass filters set at 30 to 1,500 Hz. Click rates of 19.1 clicks per second were used.

RESULTS

Pure Tone and Speech Audiometry. The pure tone audiogram (Fig 2) recorded on the 20th postoperative day revealed bilateral sensorineural hearing loss of about 80 dB. Thereafter, her hearing loss improved gradually. By the 4th postoperative month, the loss had improved to 45 dB and was stable. Speech discrimination testing using a Japanese nonsense monosyllable list at the 5th and 12th postoperative months showed an extremely poor score (0%) at 80, 90, and

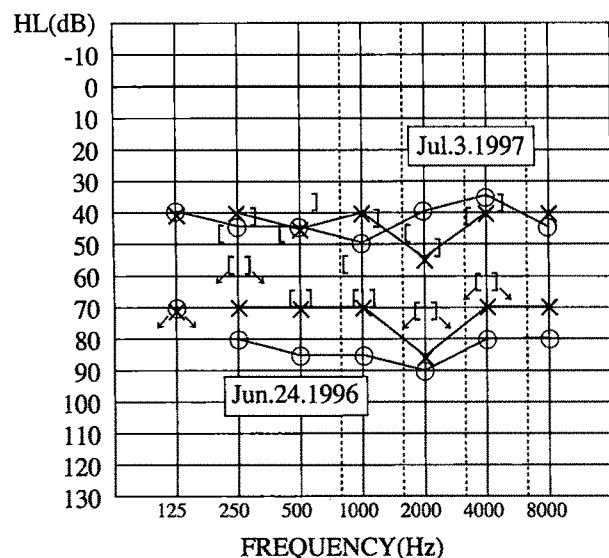


Fig 2. Pure tone audiogram recorded on 20th postoperative day (June 24, 1996) revealed bilateral sensorineural hearing loss of about 80 dB. By fourth postoperative month (July 3, 1997), loss had improved to 45 dB.

100 dB in each ear. Although the patient's verbal responses were irrelevant to the syllables, she seemed to hear the sounds.

Special Tests. The acoustic reflex threshold and decay testing data are shown in Table 1. Both ears demonstrated the presence of a normal reflex. Tone decay at 500 and 1,000 Hz in each ear was negative. In the examination of binaural localization using the warble tone, the patient identified the direction correctly 64% of the time. The same examination was performed in 6 normal volunteers (ages 24 to 37 years; 2 men and 4 women). Their mean rate of correct answers was 95.8% (range, 90% to 100%).

TABLE 1. CONTRALATERAL ACOUSTIC REFLEX THRESHOLD AND ACOUSTIC REFLEX DECAY

	Stimulus in Right Ear		Stimulus in Left Ear	
	500 Hz	1,000 Hz	500 Hz	1,000 Hz
Acoustic reflex threshold (dB HL)	DNT	90	DNT	90
Acoustic reflex decay	Negative	Negative	Negative	Negative
DNT — did not test.				

Auditory Brain Stem Response. The ABR data are shown in Fig 3 and Table 2. The absolute latencies for waves I, III, and V and the interwave latencies for I-III and I-V were normal at 80 dB on both sides. The amplitude of wave III was larger than that of wave V. Despite the profound hearing loss in both ears, wave V was well preserved, with a threshold of stimulation at 30 dB normal hearing level (nHL) on the right side and 20 dB nHL on the left.

DISCUSSION

The auditory pathway consists of several neural networks.^{1,2} There are 3 important levels at which bilateral interaction primarily occurs: the superior olivary complex (SOC), the nuclei of the lateral lemniscus, and the inferior colliculus.³ Among them, the inferior colliculus, the largest component and the target of all ascending connections from the lower nuclei, is a major auditory station in which information ascending from the lower centers must synapse. These inputs can be inhibitory or excitatory.⁴ The neurons of the inferior colliculus have more specific functions than those of the SOC, and it is well known

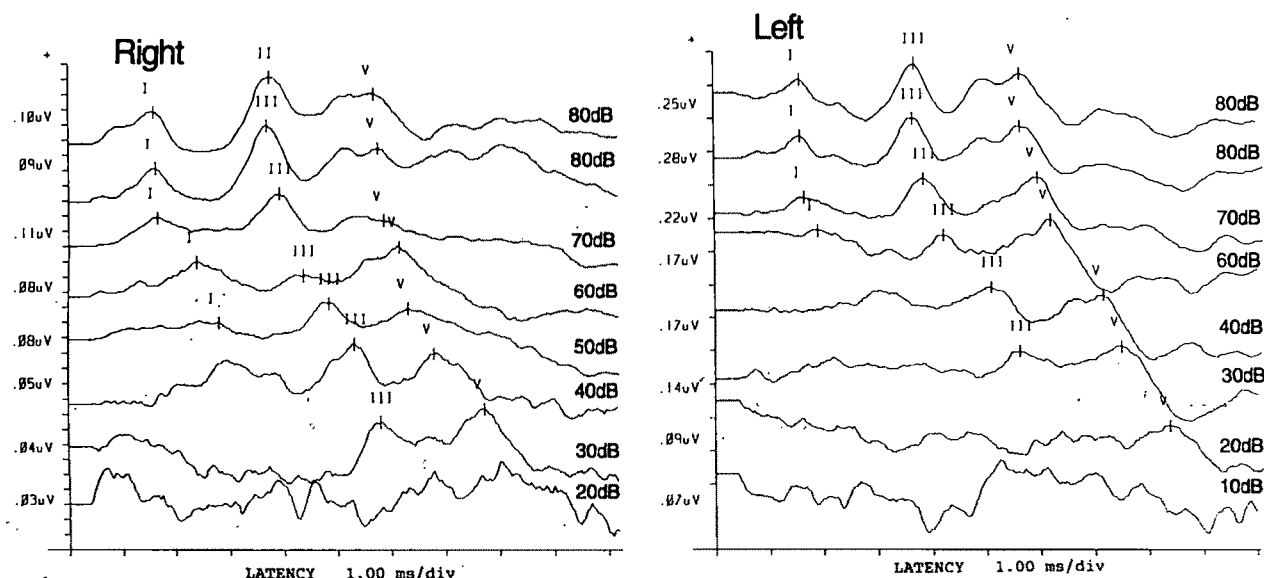


Fig 3. Surface-recorded auditory brain stem response to 80-dB normal hearing level (nHL) rarefaction clicks disclosed waves I, III, and V. There was no prolongation of latencies of these waves on either side. Amplitude of wave III was larger than that of wave V. Wave V was well preserved, with threshold of stimulation at 30 dB nHL on right side and 20 dB nHL on left side.

TABLE 2. AUDITORY BRAIN STEM RESPONSE LATENCIES

	Absolute Latency (ms)			Interwave Latency (ms)	
	I	III	V	I-III	I-V
Right	1.60	3.72	5.72	2.12	4.12
Left	1.60	3.72	5.70	2.12	4.10
Normal* (mean $\pm$ 1 SD)	1.57 $\pm$ 0.15	3.98 $\pm$ 0.45	5.92 $\pm$ 0.55	2.41 $\pm$ 0.48	4.37 $\pm$ 0.56
Stimuli were 80 dB normal hearing level.					
*In our department.					

that bilateral (not unilateral) destruction of the inferior colliculi produces clinically apparent hearing loss.³ Siebenmann⁵ described a patient with a pineal body tumor and hearing loss in 1896, and referred to this entity as midbrain deafness. In Japan, Kirikae and Satou⁶ reported a case of hearing loss following surgery for a pineal body tumor in 1957. Following advances in neuroaudiological and radiologic examinations, such as MRI, several case reports described the localization of the lesions and their audiological findings.^{1,3,7-9}

The exact anatomic site of the human auditory brain stem that generates the ABR is not known, and there is a possibility that more than one brain stem site may contribute to the waves. Ponton et al¹⁰ assumed that wave III is generated by axons emerging from the cochlear nuclei in the ventral acoustic stria and that waves IV and V reflect activity in parallel subpopulations of these ascending axons at a higher brain stem level. Several studies have determined that tumors, infarction, and radiologically caused tissue damage in the upper pons and posterior midbrain distort or eliminate waves IV and V.¹⁰ It is interesting that this case, with destruction of the inferior colliculi, disclosed normal ABR waves except for a slightly diminished wave V. To our knowledge, only 2 similar cases^{1,3} have been reported. In 1996, Meyer et al³ reported a case of pure word deafness following resection of a tectal plate glioma with a normal wave V of the ABR. In that case, the pure tone audiogram and the ABR were normal, but speech perception was severely disrupted. In 1997, Hu et al¹ reported a case of traumatic brain stem deafness with a normal ABR, in which the pure tone audiogram revealed severe hearing and speech discrimination loss. As the reason for the normal ABR, Meyer et al³ postulated that a diffuse second auditory brain stem pathway might exist outside the primary lemniscal projections. Hinman and Buchwald¹¹ called it the medial extralemniscal auditory pathway. Bogner et al¹² favored the existence of this parallel projection system in the "questionable" case of a preserved wave V of the ABR with bilateral inferior collicular destruction. It is suggested that the finding of the slightly diminished wave V in our case is consistent with the damage done to the inferior colliculus. Synchronized firing of auditory

neurons is necessary for the appearance of each wave in the ABR.^{13,14} Kaga et al¹⁵ wrote that each wave of the ABR in cats is elicited from multiple sources in the auditory brain stem nuclei and tracts, and that the main generator of P5 is both inferior colliculi. They recorded the ABR before and after aspiration of both inferior colliculi. There was no effect up to and including P4, but P5 was remarkably reduced in amplitude after aspiration. Funai and Funasaka¹⁶ reported a relationship between the activity of the inferior colliculus and each component of the ABR in rats. They wrote that there was little effect on the shape and latency of the fast waves of the ABR when the destruction was limited to the central nucleus. When the lesion was extended to or located in the lateroventral part of the inferior colliculus, in which the nerve fibers of the lateral lemniscus penetrate into the inferior colliculus, either wave V or VI was abolished. The presence of a slightly diminished wave V in our case might suggest a lesion limited to the central nucleus and involved with the lateroventral part, although part of the lesion could not be distinguished in detail on MRI.

In our case, despite a moderate sensorineural hearing loss and a normal ABR (except for some decrease of the amplitude of wave V), the speech discrimination score was 0%, and verbal comprehension was lacking. The findings at surgery and postoperative MRI led to the diagnosis of deafness due to destruction of the inferior colliculus and MGB. In cats, the ventral division of the MGB (MGv) projects to the primary and anterior auditory cortical fields. The dorsal division of the MGB (MGd) projects to the dorsal zone and the primary, secondary, anterior, and other auditory fields.^{17,18} Rauschecker¹⁹ wrote that the projection pattern from the inferior colliculus via the MGB to the auditory cortex could reflect a separation of function that processes spatial and pattern sound attributes in the auditory system of rhesus monkeys. Olsen and Suga^{20,21} and Olsen and Rauschecker²² found that neurons in the monkey MGd are sensitive to species-specific communication sounds and specific for delay-tuned combination sounds and social communication signals. He and Hashikawa²³ described the possibility that the auditory projection pathway through the MGd in animals may be in-

involved in complex auditory information processing. Hashimoto²⁴ showed that some MGB neurons act as the formant detector in conscious guinea pigs. Kraus et al²⁵ reported that synthesized characteristic speech contrasts elicited a strong mismatch response from the caudomedial portion of the medial geniculate nucleus in guinea pigs. Tanaka and Taniguchi²⁶ recorded one MGB neuron in guinea pigs that did not respond to pure tones but showed a strong excitatory response to a vocalized sound. They wrote that MGB neurons selective for species-specific sounds may have a major role in the neural mechanism for processing communication sounds. In our case, the lesion of the MGB may have caused the severe impairment in speech perception.

Compared with that in normal subjects, the sound localization in this patient was impaired. Both afferent auditory pathways in the lower brain stem and their connection to the facial nerve pathway were considered to be intact, because the acoustic reflex threshold and decay testing results were normal. There is a possibility that a lesion of the inferior colliculus and/or the MGB may impair sound localization. It is known that neurons involved in analyzing interaural time or level differences are abundant in the central inferior colliculus and subdivisions of the SOC. Thus, an intact SOC suffices for analysis of interaural time or level differences to localize at least nonverbal sound.³ Kuwada et al²⁷ reported that feline inferior colliculus neurons responded selectively to a change of direction and rate of interaural phase in a study using binaural beat stimuli; this finding suggests a direction or speed sensitivity. Aitkin and Jones²⁸ reported the possible existence of processing channels

for sound localization between the feline colliculus and cortex. Imig et al²⁹ described a mechanism for neural sensitivity to sound localization in the cat MGB, whereas Kelly and Judge³⁰ reported that rats with complete bilateral MGB destruction could localize sounds. Our case suggests that the inferior colliculus and/or MGB participates in sound localization in humans.

The sensorineural hearing loss of this patient was 80 dB, which improved to 45 dB during the 4-month period after surgery. One possible explanation for this improvement may be the reduction of the influence of postoperative brain edema. However, the patient disavowed any awareness of a change in subjective verbal sound discrimination accompanying the improvement in the hearing loss. Further, she became able to perceive some new sounds during the first year after surgery. This outcome suggests a possible acquirement in nonverbal sound recognition.

Various hearing disturbances can occur in association with upper brain stem and MGB destruction, and the findings of pure tone audiometry are not always consistent with those of speech audiometry. Compared with the visual system, much less information exists about the functional specialization of the multiple central auditory system maps. An understanding of central auditory representations seems necessary to an understanding of higher auditory processing, including speech and auditory space perception.¹⁹ This case suggests that the inferior colliculus and MGB play an important role in speech perception and sound localization, and affords some speculation about the generator of the ABR.

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FUNCTIONAL ENDOSCOPIC SINUS SURGERY IN CHILDREN AND ADULTS

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Functional endoscopic sinus surgery (FESS) has become a popular procedure for the treatment of adults with chronic sinusitis. Recently, it has also been applied in the pediatric population. It has been used to treat chronic sinusitis in our department since April 1988. As of March 1998, 1,112 patients were available for analysis by file and questionnaire review. Of the 1,112 patients, 104 patients (9.4%) who were 16 years of age or younger at the time they first underwent FESS in our department were included in the pediatric endoscopic sinus surgery (PESS) group. The other 1,008 patients (90.6%) were included in the ordinary FESS group. In total, 121 PESS and 1,106 (adult) FESS operations were performed on these patients. Operative complications occurred in 5 PESS operations (4.1%) and 116 FESS operations (10.5%). The postoperative improvement rate was 84% in PESS and 77.1% in FESS. We conclude that PESS can be applied to treat chronic sinusitis effectively in the pediatric population and with less morbidity than FESS.

KEY WORDS — adults, children, chronic sinusitis, functional endoscopic sinus surgery.

INTRODUCTION

Since functional endoscopic sinus surgery (FESS) was introduced by Kennedy et al,¹ it has become a popular procedure for the treatment of chronic sinusitis in adults.² Its safety and efficacy have been evaluated in many reports. Generally speaking, FESS is considered to be a relatively safe and effective procedure for treating chronic sinusitis with or without nasal polyps in adults.³

In 1989, Gross et al⁴ reported their experience with the application of FESS in the pediatric age group. Since then, FESS has rapidly gained acceptance as the primary surgical procedure for the treatment of chronic sinusitis in children.⁵ Because of its possible differences from ordinary FESS used in the adult population, Poole⁶ suggested use of the term pediatric endoscopic sinus surgery (PESS) rather than FESS to mean FESS performed in the pediatric population.

Although PESS procedures are similar to those of FESS in adults,² PESS is considered to be more difficult because of the smaller anatomy of children.⁷ However, with the help of enhanced illumination and the angled, magnified views of endoscopes, PESS can be relatively safely performed.¹ The present literature provides evidence that PESS is an effective procedure for the treatment of chronic sinusitis in children, but long-term results yielding firm conclusions have yet to be reported.⁸ In this study, we compared our experiences with FESS in children and in adults after a mean follow-up period of 3¹/₂ years.

MATERIALS AND METHODS

Functional endoscopic sinus surgery has been used

to manage chronic sinusitis patients with or without polyps in our department since 1988. The indication for FESS was the failure of medical treatment for these patients. The definition of "failure of medical treatment" was unsatisfactory results after repeated and appropriate antibiotic therapy with adequate auxiliary treatment. "Repeated and appropriate antibiotic therapy" meant long-term antibiotic management or several courses of antibiotic management based on the results of bacterial cultures. Based on the clinical course and findings, some auxiliary treatment was added. The auxiliary treatment included mucolytic agents, antihistamines, nasal steroids, and nasal douche. Further, the indications for revision PESS or FESS were the same as those for primary surgeries, ie, unsatisfactory results after repeated and appropriate antibiotic therapy with adequate auxiliary treatment.

Those patients who underwent FESS in our department between April 1988 and March 1998 were included in this study. In total, 1,112 patients were available for analysis by file and questionnaire review. These 1,112 patients were divided into pediatric and adult groups according to the age at which they underwent FESS or the age at which they first underwent FESS in our department. Patients 16 years of age or younger were included in the PESS group, and patients 17 years old or older were included in the FESS (ie, adult FESS) group. Questionnaires asking about postoperative symptoms were mailed to all the patients to assess the effect of FESS in the treatment of chronic sinusitis with or without polyps. The symptoms were classified as 1) no symptoms, 2)

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TABLE 1. AGE DISTRIBUTION

Age (y)	No. of Patients
5	4
6	5
7	2
8	1
9	11
10	2
11	7
12	12
13	10
14	12
15	11
16	27
17-24	160
25-34	225
35-44	197
45-54	123
55-64	132
65-74	153
75-84	18

symptoms that improved after surgery, 3) symptoms that were unchanged, and 4) symptoms that worsened. Improvement of sinusitis was defined as absence of symptoms or symptoms' having improved after FESS.

RESULTS

Among the 1,112 treated patients, 104 patients (9.4%) belonged to the PESS group, and the other 1,008 patients (90.6%) to the ordinary FESS group. In the PESS group, the ages of the patients ranged from 5 to 16 years old, with a mean age of 12.6 years. Fifty-five of these children were boys, and the remaining 49 were girls. In the FESS group, the ages ranged from 17 to 84 years old, with a mean age of 43.4 years. Six hundred forty patients were men, and the remaining 368 patients were women. The age distribution is shown in Table 1.

Altogether, 121 PESS operations were performed on the 104 PESS-treated patients. The indications for PESS were chronic sinusitis without polyps in 63 operations, nasal polyps in 47 operations, and antrochoanal polyps in 11 operations. Of the operations, 102 were bilateral, and the other 19 were unilateral. Thirty-six operations were performed under local anesthesia, and the remaining 85 operations were performed under general anesthesia.

A total of 1,106 FESS operations were performed on the 1,008 FESS-treated patients. The indications for FESS were chronic sinusitis without polyps in 565 operations, nasal polyps in 515 operations, and antrochoanal polyps in 26 operations. Bilateral operations were performed in 855 cases, and unilateral

operations in 251. Six hundred ninety-three operations were done under local anesthesia, and 413 were done under general anesthesia.

One hundred five PESS operations were primary, and the remaining 16 were revision operations. The indications for revision PESS were chronic sinusitis without polyps in 10 operations and nasal polyps in 6 operations. Nine hundred eighty FESS operations were primary, and 126 were revision operations. The indications for revision FESS were chronic sinusitis without polyps in 86 operations; nasal polyps in 39 operations, and antrochoanal polyps in 1 operation.

The patients in 5 PESS operations (4.1%) experienced operative complications. Among them, 2 patients had chronic sinusitis without polyps, another 2 patients had nasal polyps, and the last had antrochoanal polyps. Diplopia due to orbital penetration occurred in 1 case. Orbital fat was extruded in 2 cases. Blood was transfused in 1 case. The operation was stopped in the last case because of bleeding.

In contrast, operative complications occurred in 116 FESS operations (10.5%). Among them, the indications for FESS were chronic sinusitis without polyps in 53 operations, nasal polyps in 60 operations, and antrochoanal polyps in 3 operations. The most common complication in the FESS group was orbital fat extrusion (35 cases). Blood transfusion was given after 26 operations. Epistaxis occurred in 25 cases. The FESS was stopped in 8 operations because of pain. The periorbital was exposed in 7 cases, and the dura in 2. Atrophic rhinitis followed FESS in 1 patient. Nasal packs were left in the ethmoid cavity in 1 patient. More severe complications occurred in 11 operations. Cerebrospinal fluid leakage occurred in 3 cases. Diplopia that resulted from orbital injury occurred in 2 operations. Nasolacrimal duct injury followed FESS in 6 cases. The difference in complication rates between PESS and FESS was statistically significant ($p = .026$). The operative complications for each indication are shown in Table 2.

Follow-up questionnaires were answered effectively by 50 PESS patients. Among patients with chronic sinusitis without polyps, 4 reported no symptoms at all, 13 indicated that the symptoms had improved, 3 considered the symptoms to be the same as before surgery, and 2 complained that the symptoms had worsened. Among patients with nasal polyps, 3 reported no symptoms at all, 16 indicated that the symptoms had improved, 2 considered the symptoms to be the same as before surgery, and 1 complained that the symptoms had worsened. Among patients with antrochoanal polyps, 1 reported no symptoms at all, and 6 indicated that the symptoms had improved. The improvement rate of PESS was 84%

TABLE 2. REVISION SURGERY, OPERATIVE COMPLICATIONS, AND PROGNOSIS BY INDICATIONS FOR SURGERY

	PESS (121*)						FESS (1,106)					
	Chronic Sinusitis (63*)		Nasal Polyps (47)		Antrochoanal Polyps (11)		Chronic Sinusitis (565)		Nasal Polyps (515)		Antrochoanal Polyps (26)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Revision surgery	10	8.3	6	5.0	0	0	86	7.8	39	3.5	1	0.1
Operative complications	2		2		1		53		60		3	
Orbital fat extrusion	1		1				21		14			
Transfusion	1						5		20		1	
Epistaxis			1				10		14		1	
Pain							3		5			
Periorbital exposure							5		2			
Nasolacrimal duct injury							3		2		1	
Cerebrospinal fluid leakage							2		1			
Diplopia			1		1		1					
Dura exposure							1		1			
Left packs							1					
Atrophic rhinitis							1					
Improvement	17	78.0	19	86.4	6	100.0	185	70.9	188	83.6	10	90.9

PESS — pediatric (functional) endoscopic sinus surgery; FESS — functional endoscopic sinus surgery (in adults).

*Number of operations.

(42/50 patients). The follow-up period ranged from 7 months to 9 years 2 months, with a mean of 3 years 7 months.

Follow-up questionnaires were answered effectively by 497 FESS patients. Among patients with chronic sinusitis without polyps, 25 reported no symptoms at all, 160 indicated that the symptoms had improved, 56 considered the symptoms to be the same as before surgery, and 20 complained that the symptoms had worsened. Among patients with nasal polyps, 30 reported no symptoms at all, 158 indicated that the symptoms had improved, 28 considered the symptoms to be the same as before surgery, and 9 complained that the symptoms had worsened. Among patients with antrochoanal polyps, 2 reported no symptoms at all, 8 indicated that the symptoms had improved, and 1 complained that the symptoms had worsened. The improvement rate of FESS was 77.1% (383/497). The follow-up period ranged from 7 months to 10 years 6 months, with a mean of 3 years 8 months. The difference in improvement rates was not statistically significant between the PESS and FESS groups ($p = .262$).

DISCUSSION

Since FESS was first introduced in the United States to treat chronic sinusitis in adults, long-term results have been reported to confirm its effectiveness.⁹ Moreover, the preliminary results of PESS also provide evidence of its efficacy for the treatment of chronic sinusitis in children.⁸ However, the underlying causes of pediatric sinusitis are different from

those of adult sinusitis.¹⁰ Therefore, the indications for FESS might not be applicable to PESS. Poole⁶ proposed that PESS should be used in a more conservative way. In our study, the ratio of PESS to FESS was 9.4% to 90.6%. In contrast, Lazar et al¹¹ performed PESS and FESS in a ratio of 33.6% to 66.4% among 773 consecutive chronic or recurrent sinusitis patients who underwent endoscopic sinus surgery in a period of about 3½ years. The frequency of performance of PESS as compared with FESS was statistically lower in our series than in the series of Lazar et al ($p < .001$). This is at least partly because we treated pediatric sinusitis in a more conservative way. Besides maximal medical treatment, more time was taken to see the progress of pediatric sinusitis before the decision to perform PESS was made.

The PESS procedures we performed were similar to those of FESS. However, the extent of surgery was based on the findings of computed tomography. Since the frontal and sphenoid sinuses are less developed in children than in adults, frontal and sphenoid sinuses were less frequently opened in PESS than in FESS in our cases. The natural ostia of the frontal and sphenoid sinuses were not opened further in Lusk and Muntz's endoscopic sinus surgery in children with chronic sinusitis,¹² but we did identify and enlarge the natural ostia of the frontal and sphenoid sinuses if computed tomographic scans showed disease in these sinuses. Obviously, PESS needs to be performed under general anesthesia more often than FESS, because children are less cooperative than adults.⁷ Although PESS should generally

be performed with pediatric operative instruments,^{5,7} we did all of our PESS with adult instruments without difficulty, as did Lazar et al.¹¹ However, it is clear that the use of adult instruments is not appropriate in infants and very young children.⁵

Hebert and Bent⁸ performed a meta-analysis of the literature and found a major complication rate of 0.6% in PESS. They concluded that PESS is a relatively safe treatment for chronic sinusitis. The operative complication rate of 4.1% found in our PESS procedures was statistically lower than the operative complication rate of FESS ($p = .026$), perhaps because PESS was most frequently performed by the more senior surgeons in our department.

Postoperative care is a very important determinant for the prognosis of PESS.¹⁰ Usually, a second nasal endoscopy under general anesthesia is considered necessary for good results with PESS.⁴ However, recent reports have provided evidence that second-look nasal endoscopy does not improve the prognosis of patients undergoing PESS.^{13,14} A second-look nasal endoscopy under general anesthesia was not performed in our PESS cases, either. However, the improvement rate of 84% in our PESS cases was comparable not only to that of our FESS cases (77.1%), but also to the improvement rate reported in the literature for PESS.⁸

In this study, the indications for PESS and FESS were divided into chronic sinusitis, nasal polyps, and antrochoanal polyps. However, patients with antrochoanal polyps were too few for us to evaluate the influence of antrochoanal polyps on PESS and FESS. Among the 3 indications, chronic sinusitis was the

most common indication for both PESS and FESS. Although the frequencies of revision PESS and revision FESS were not significantly different, revision FESS was performed more often for chronic sinusitis than for nasal polyps ($p < .001$). Similarly, although the improvement rates of PESS and FESS were not significantly different, the prognosis of FESS was better in patients with nasal polyps than those with chronic sinusitis ($p = .001$). Despite a tendency for recurrence, nasal polyp patients seemed to be satisfied with the results of FESS and underwent fewer revision procedures. On the other hand, although the frequencies of operative complications of FESS were not significantly different between chronic sinusitis and nasal polyp patients, nasal polyp patients tended to bleed during FESS. Epistaxis occurred and blood was transfused more often in nasal polyp patients than in chronic sinusitis patients ($p = .002$). Therefore, more effort is needed to prevent bleeding in nasal polyp patients who undergo FESS.

CONCLUSIONS

This study collected the data of 104 pediatric sinusitis patients on whom 121 PESS operations were performed and 1,008 adult sinusitis patients on whom 1,106 FESS operations were performed. An operative complication rate of 4.1% was found in PESS procedures, and one of 10.5% in FESS procedures. After a mean follow-up period of 3 years 7 months, an improvement rate of 84% was obtained in our PESS patients. After a mean follow-up period of 3 years 8 months, an improvement rate of 77.1% was obtained in our FESS patients. It is concluded that PESS is as safe and effective a procedure as FESS.

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TOTAL INFERIOR TURBINECTOMY: OPERATIVE RESULTS AND TECHNIQUE

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The internal nasal structures, including the turbinates, regulate the nasal airflow. The surgical treatment of turbinate hypertrophy remains controversial. A wide variety of surgical procedures is performed, with universally unsatisfactory results. Interference with nasal physiology and possible postoperative complications have been the main reasons for the objection to total inferior turbinectomy. Over a 6-year period, 357 total inferior bilateral turbinectomies were performed at our institution. We present the results of these procedures and describe our surgical technique. We conclude that even in a hot and dusty climate, total inferior turbinectomy is an effective and relatively safe procedure.

KEY WORDS — nasal obstruction, total inferior turbinectomy.

INTRODUCTION

Nasal airway obstruction is a very common condition, even in the absence of overt obstructive disease such as nasal polyps. The inner nasal structures, the nasal septum and nasal turbinates, are responsible for regulating the amount, humidity, and temperature of the airflow.¹⁻³ There is general agreement among rhinologists in regard to the treatment of septal deviation and nasal malformations. The treatment of turbinate malfunction and hypertrophy is, however, controversial. A wide variety of surgical procedures are performed upon the inferior turbinates, with universally unsatisfactory results.^{2,4} The frustration due to the lack of a satisfactory surgical solution for nasal airway obstruction has urged surgeons to attempt a more radical operation, the total inferior turbinectomy. During the past 15 years, we have seen numerous publications debating this issue. Many surgeons do not approve of the performance of this operation. Any surgical procedure performed upon the nasal turbinates is certain to interfere with their physiological function. This and the possibility of postoperative complications are the reasons for the controversial attitudes toward this operation.^{1,2,5-7} Being unable to offer a better solution, we began, in 1980, to perform total inferior turbinectomies in a few selected patients. Our good results and encouraging announcements in the medical literature^{2,3,8,9} convinced us to carry on with the procedure and to improve our surgical technique. We perform total inferior turbinectomy alone or in conjunction with other operations on the nose or the paranasal sinuses.

The purpose of this paper is to share our experi-

ence and to focus attention upon the surgical technique we use and the measures we take to reduce complications.

MATERIALS AND METHODS

Between the years 1986 and 1991, 357 patients underwent total inferior turbinectomy. All patients suffered from chronic nasal obstruction and failed to respond to local and systemic treatment. The youngest was an 8-year-old girl, and the oldest was a 77-year-old man. One hundred two patients underwent inferior turbinectomy as the only surgical procedure performed. In 255 patients, the operation was performed as part of combined surgery: in 225 patients, in conjunction with nasal septal surgery, and in 30 patients, in conjunction with nasal polypectomy, 4 of whom also underwent an antral procedure. The vast majority of the patients underwent the operation under local anesthesia, but since 1990, we have preferred general anesthesia as our first choice. Regardless of the type of anesthesia, the nose is prepared before the operation with nasal packing soaked with a solution of lidocaine hydrochloride 2% and epinephrine 1:100,000 for 10 minutes. This packing causes shrinkage of the mucosa, enabling better visualization of the interior of the nose, which is the key to an easy and safe procedure. We use a high-power fiberoptic headlamp with adjustable focus.

We inject the submucosa of the inferior nasal turbinate with the solution mentioned above. The posterior end of the turbinate is the most difficult to inject. We overcome this difficulty by using a disposable syringe with a 23-gauge, 3.5-inch spinal needle.

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This long, thin needle enables the surgeon to inject any point within the nose under direct vision. Turbinate surgery is much easier when done in conjunction with septal surgery. The mobility of the septum allows it to be moved to the opposite side with the nasal speculum, and thus, more room for visualization and maneuvering is obtained. The turbinate is then crushed along its line of attachment to the lateral nasal wall and almost simultaneously is fractured in a superior direction. Thus, the turbinate actually remains hanging only by its layers of mucosa. This is a very important maneuver that serves 3 goals:

1. It serves as a test for the effectiveness of the local anesthesia before scissors are used.
2. The crushing of the turbinate and the fracturing of its bone make it very easy to trim the turbinate and also avoid possible bleeding.
3. Turning the fractured turbinate upward along its anteroposterior axis makes it possible to visualize and anesthetize the posteroinferior part of the turbinate, an area that is very difficult to reach otherwise.

Via this technique, the turbinate is then trimmed with the turbinate scissors. The turbinate comes off relatively easily, usually in one piece. Attention must be given at this point to the possibility that the trimmed turbinate might slip posteriorly into the throat. Once the turbinate has been removed, attention should be paid to possible bleeding. Using a suction cauterizer (isolated except for its tip), we electrocauterize the base of the excised turbinate, beginning anteriorly and following its line posteriorly. Thus, any existing bleeding flows posteriorly, allowing the surgeon to see its source and electrocauterize it. After both sides are done, the nose is then packed for 3 to 4 days. For packing, we formerly used absorbable gelatin sponge (Gelfoam) pressed to the lateral wall by packed gauze, in order to prevent potential late bleeding that might occur spontaneously or as a result of the removal of the regular nasal packing. We now use Meroçel nasal packing to which we suture gelatin sponge. This "double" nasal packing is inserted with the gelatin sponge facing the lateral wall of the nose.

RESULTS

A total of 351 patients (98.3%) underwent the operation without any significant complication. Six patients (1.7%) experienced postoperative hemorrhage that required emergency intervention. Two of the above experienced delayed hemorrhage: one on the fifth postoperative day, and one on the ninth postoperative day. Two patients required revision of inferior turbinectomy, and 4 underwent reexcision of na-

sal polyps. All patients were followed for 6 years.

Evaluation of the success of the operation was done on a subjective basis. Each patient was asked to answer the following identical questions twice, once 6 months after surgery and again 1 year later:

1. Has your nasal breathing improved?
2. Do you use any medications to relieve nasal symptoms?
3. Have you suffered from any nasal side effects after the operation?
4. Can you mention any other changes caused by the operation?
5. Are you satisfied with the results of the operation?

Six months after the operation, the following results were obtained:

1. All but 9 patients answered the first question positively.
2. None of the patients used any medication for the relief of nasal symptoms.
3. Eight patients complained of nasal crusting, and 11 patients mentioned some discomfort or pain in the nose.
4. Forty-five patients reported improvement in a series of complaints including poor quality of sleep, difficulty during physical exercising, and headaches.
5. The last question was answered positively by 348 patients.

At 18 months after surgery, the answers were very much the same in regard to nasal breathing and overall satisfaction. Different answers were obtained regarding nasal crusting. Three patients still complained of nasal crusts, but when asked specifically, 12 patients answered positively. Seven patients required treatment for nasal symptoms; all of them belonged to the group that underwent nasal polypectomy. Four of these patients required reexcision of nasal polyps during the 6-year follow-up period.

DISCUSSION

Total removal of the inferior turbinate is an accepted surgical procedure for the relief of chronic nasal obstruction. Surgeons hesitate to use it for two main reasons: 1) total turbinectomy is not "physiologic"; 2) the procedure is not "safe." As for the interference of the operation with the physiology of the nose, this might be true for healthy people. We, instead, operate on patients with nasal obstruction

who are unable to use their noses for breathing. The term "physiologic" in this connection is inappropriate, and the term "pathological" should be considered. The results show clearly that the vast majority of patients who undergo this operation do enjoy its outcome and are better off after the operation.

As for the safety of total inferior turbinectomy, the major complication is bleeding. We have described the technique we use to reduce bleeding. In our series, we experienced bleeding in only 6 patients out of 357 (1.7%). We believe that using the combined Merocel-Gelfoam packing, and avoiding operating on patients who are taking anticoagulants of any kind, can lower this percentage even more. However, this small percentage is "acceptable," and therefore, the possibility of bleeding should not be considered a contraindication for total inferior turbinectomy.

We strongly advise the absolute restriction of any medication containing aspirin or anti-inflammatory nonsteroidal drugs for at least 10 days before the operation. We found that 4 of the 6 patients with postoperative bleeding did use such medications.

Ozena (atrophic rhinitis) is believed by some to be related to total inferior turbinectomy. This is a serious disease that may discourage surgeons from performing the operation. In our series, conducted in a hot, dusty climate, no such complication was observed, nor did we find any documented case in the literature. We therefore cannot regard ozena as a possible complication of this operation.

We conclude that total inferior turbinectomy is an effective and relatively safe procedure, and using the described technique makes it even safer.

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TIME COURSE OF CHANGES IN ABSORPTION OF MACROMOLECULE THROUGH THE NASAL MUCOSA AFTER ANTIGEN CHALLENGE IN GUINEA PIG MODEL OF ALLERGIC RHINITIS

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The time course of changes in absorption of horseradish peroxidase (HRP) through the nasal mucosa after antigen challenge was evaluated in a guinea pig model of allergic rhinitis immunized with ovalbumin. Before and at 5 minutes, 4 hours, and 24 hours after nasal antigen challenge, both nasal cavities were filled with 5% HRP solution for 30 minutes, and blood was obtained to measure serum HRP levels by enzyme-linked immunosorbent assay. In immunized animals, the serum HRP levels were 2.3 times higher than those of normal controls ($p < .05$) before antigen challenge, which was performed 7 days after a series of nasal antigenic sensitizations. At 5 to 35 minutes after antigen challenge, the HRP levels decreased to one sixth of the prechallenge levels ($p < .05$), and they did not show a difference from the control levels. However, they increased markedly at 4 and 24 hours after antigen challenge ($p < .01$). The present study suggests that the absorption of macromolecules through the allergic nasal mucosa is enhanced markedly, depending upon the time course after antigen challenge, although it shows no apparent difference from normal controls during the dominant exudative process.

KEY WORDS — allergic rhinitis, epithelial permeability, guinea pig, horseradish peroxidase, nasal mucosa.

INTRODUCTION

The responses of the nasal mucosa to histamine and other chemical mediators applied on the nasal mucosa are significantly enhanced in patients with allergic rhinitis as compared to normal controls. Reactivity of the nasal mucosa to histamine in subjects with pollinosis is also significantly enhanced during the pollen season.¹ A number of hypotheses have been advanced to explain the mechanism of this hyperreactivity of the nasal mucosa to histamine. One is enhanced permeability of the nasal epithelium to histamine due to an impaired barrier function of the epithelial layer induced by functional changes of epithelial tight junctions^{2,3} and/or by morphological changes of the epithelial cells with widening of the interepithelial spaces.⁴ In patients with bronchial asthma, epithelial damage of the bronchial mucosa that is apparent by light microscopy has been reported,⁵⁻⁹ but this finding remains controversial.¹⁰ In patients with allergic rhinitis, epithelial damage is not apparent, at least by light microscopy. However, the incidence of electron microscopic degeneration of nasal epithelial cells with widening of intercellular spaces is significantly higher in patients with allergic rhinitis than in normal controls.¹¹ Reports in the literature conflict regarding changes of the inward permeability of the allergic nasal mucosa to various molecules. A number of au-

thors have reported increased nasal permeability to macromolecules (antigen, albumin, and horseradish peroxidase [HRP]) in patients with allergic rhinitis and in animal models.^{2,3,12,13} In an immunohistologic study by Kawaguchi et al,² histamine increased the permeability of the nasal epithelium to HRP in both immunized and nonimmunized guinea pigs, although the degree of increase in epithelial permeability was significantly greater in the immunized animals. Numerous previous studies have suggested that antigens, chemical mediators, cigarette smoke, and ozone significantly enhance the inward permeability of the tracheobronchial mucosa to macromolecules in both immunized and nonimmunized animals and in human subjects.¹⁴⁻²² These stimuli were considered to cause perturbation of epithelial tight junctions and the formation of intercellular channels for the passage of molecules from the airway lumen.^{15,21,22} In contrast, Okuda²³ and Cohen et al²⁴ reported decreased inward permeability of the nasal mucosa to macromolecules in patients with allergic rhinitis, while Persson and his group^{10,25,26} reported that the rate of absorption of chromium 51-ethylenediaminetetraacetic acid through the nasal mucosa was not significantly enhanced in subjects with allergic rhinitis, either during the airway mucosal exudation process or during the immediate postexudation phase induced by chal-

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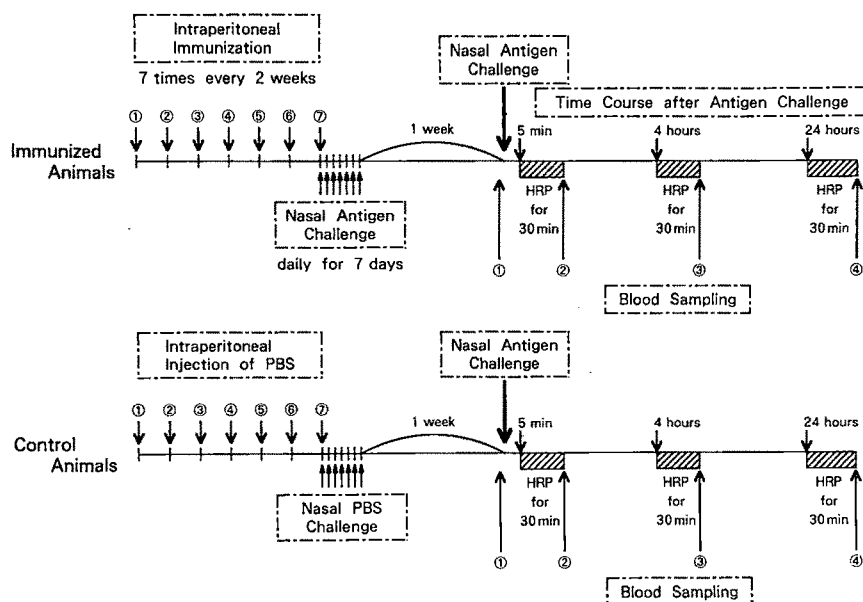


Fig 1. Time schedule for evaluating effect of antigen challenge on absorption of horseradish peroxidase (HRP) through nasal mucosa in guinea pig model of allergic rhinitis compared to normal controls. PBS — phosphate-buffered saline solution.

lenges with antigen and various chemical mediators on the nasal mucosa. The purpose of this paper is to analyze the time course of changes in absorption of HRP through the nasal mucosa after rather intense antigen challenge on the nasal mucosa in an ovalbumin-immunized guinea pig model of allergic rhinitis that shows only an immediate phase reaction.

MATERIAL AND METHODS

Figure 1 shows the time schedule of the experiment. Sixty-four male Hartley guinea pigs weighing 450 to 500 g were divided into allergic and nonallergic groups. Thirty-two animals were immunized 7 times every 2 weeks by intraperitoneal injections of a mixture of 20 μ g of ovalbumin and 10 mg of aluminum hydroxide gel dissolved in 1 mL of phosphate-buffered normal saline (PBS) solution. After the last intraperitoneal immunization, the immunized animals received an instillation of 20 μ L of 5% ovalbumin-dissolved PBS solution into both nasal cavities daily for 7 days. As reported in our previous article,²⁷ this immunization caused a significant increase in antigen-specific serum IgE and IgG levels, and a single antigen challenge in this animal model caused prominent sneezing, watery rhinorrhea, and nasal obstruction only in the immediate phase and not in the late phase, although it caused a significant increase in eosinophils in the nasal mucosa from 3 to 24 hours after antigen challenge. The 32 nonimmunized control animals received intraperitoneal injection and nasal instillation of the same amount of PBS solution following the same time schedule as the immunized animals. Seven days after the last nasal instillation of ovalbumin solution in the immunized animals and PBS solution in the control animals, 20 μ L of 5%

ovalbumin solution was instilled into both nasal cavities in both the immunized and nonimmunized control animals. The immunized and nonimmunized groups were each divided into 4 subgroups, each subgroup consisting of 8 animals. All animals were anesthetized intraperitoneally with sodium pentobarbital (50 mg/kg, Abbott, North Chicago, Ill) just before nasal instillation of HRP. For nasal instillation of HRP solution, the intravenous cannula with a catheter (Vasculon 2, 14 gauge, 45 mm, BOC Ohmeda AB, Helsingborg, Sweden), which was cut to 4 mm, was connected to a 1-mL disposable syringe via a 3-way stopcock (Terfusion, Termo, Tokyo, Japan). A pair of cannulas connected to the syringe, filled with a 5% unlabeled HRP (type 4; Sigma Chemical Co, St Louis, Mo)—PBS solution, were inserted into both nostrils and were fixed with surgical glue (Histoacryl glue, Muranaka, Tokyo, Japan). We instilled 80 μ L of HRP solution into both nasal cavities before antigen challenge in the first group, at 5 minutes after antigen challenge in the second group, at 4 hours after antigen challenge in the third group, and at 24 hours after antigen challenge in the fourth group. After instillation of the HRP, the stopcocks connected to the catheters were closed, and the catheters were left in place to prevent leakage of HRP. All animals were kept in a 45° head-down position during instillation of HRP and for 30 minutes afterward to prevent swallowing or aspiration of the HRP. Thirty minutes after the nasal instillation, the HRP solution in the nasal cavities was removed by suction, and blood was obtained by cardiac puncture in each animal. The blood was centrifuged, and serum was obtained and stored at -80°C. The HRP concentration in the serum was determined by an enzyme-linked immunosorbent assay. Rabbit anti-HRP antibody was diluted

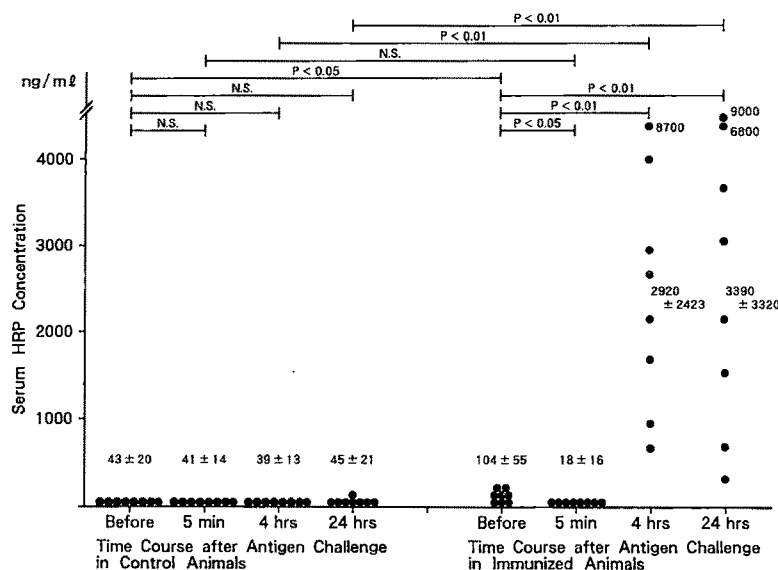


Fig 2. Effect of antigen challenge on serum levels of HRP absorbed through nasal mucosa in guinea pig model of allergic rhinitis compared to normal controls. In normal controls, antigen challenge on nasal mucosa did not affect absorption of HRP through nasal mucosa. However, in immunized animals, serum HRP levels varied significantly, depending upon time course after antigen challenge.

1:1,000 in carbonate buffer (pH 9.6), and 100 μ L was spread onto polyvinyl chloride microtiter plates and left overnight at 4°C. The plates were then washed 3 times with PBS solution containing 5% fetal calf serum at room temperature for 2 hours. After being washed, the wells were filled with 100 μ L of 1:100 diluted samples in PBS solution containing 5% fetal calf serum and Tween 20. The plates were incubated for 2 hours at 37°C. After being washed again, each well was developed for color with 200 μ L of 0.04% *O*-phenylenediamine in citrate-phosphate buffer (pH 5.0), and the optical density at 490 nm was determined with an automated microplate reader. An HRP standard curve was generated with serially diluted HRP in PBS solution containing 1% normal nonimmunized guinea pig serum. The concentration of HRP was obtained from the standard curve with a sensitivity of 5 ng/mL.

DATA ANALYSIS

The data are shown as means $\pm$ standard deviations. A 1-factor analysis of variance and a Mann-Whitney test were used to determine statistical significance.

RESULTS

Figure 2 shows the concentrations of serum HRP obtained before and after a single antigen challenge in each of the immunized and control groups. The serum HRP concentration in the control animals was 43 $\pm$ 20 ng/mL before antigen challenge and 41 $\pm$ 14 ng/mL, 38 $\pm$ 13 ng/mL, and 45 $\pm$ 21 ng/mL at 5 minutes, 4 hours, and 24 hours after the single antigen challenge, respectively. No differences were observed in serum HRP levels among the 4 subgroups. In the immunized animals, the serum HRP level before antigen challenge was 104 $\pm$ 55 ng/mL, which was significantly ($p < .05$) higher than the level in the con-

trol group before antigen challenge. However, at 5 minutes after antigen challenge, the serum HRP level was 18 $\pm$ 16 ng/mL, which was significantly lower ($p < .05$) than the level before antigen challenge in the immunized group and not different from the serum HRP level in the control group. At 4 and 24 hours after antigen challenge, the serum HRP levels in the immunized animals had increased markedly, to 2,920 $\pm$ 2,423 ng/mL and 3,390 $\pm$ 3,320 ng/mL, respectively. The differences from both the control group and from the immunized group before antigen challenge were statistically significant ($p < .01$).

DISCUSSION

The present study showed that in our guinea pig model of allergic rhinitis, absorption of HRP through the nasal mucosa was significantly increased before antigen challenge, and that from 5 to 30 minutes after antigen challenge, the nasal mucosa showed a transient but significant decrease in HRP absorption as compared to immunized animals before antigen challenge; serum HRP levels did not show any difference from normal controls. This is consistent with the findings of Persson et al.^{10,25,26} The dominant flux of the plasma components from the interstitium to the airway lumen, which was induced by various chemical mediators in the nasal mucosa, seems to have inhibited absorption of the HRP through the nasal epithelium into the microvasculature. However, absorption of the HRP through the nasal mucosa was markedly enhanced at 4 and 24 hours after nasal antigen challenge as compared both to nonimmunized animals after antigen challenge and to immunized animals before antigen challenge. The enhanced absorption of HRP through the nasal mucosa observed 7 days after a series of nasal sensitizations with antigen and at 4 to 24 hours after nasal antigen challenge cannot be

attributed to functional perturbation of tight junctions induced by chemical mediators,² because the functional effect of chemical mediators on tight junctions cannot be considered to continue so long.¹⁴ This enhanced absorption may be related to the morphological changes of intercellular spaces observed in our animal model.²⁸ In another morphological study, we counted the number of degenerated epithelial cells by electron microscopy among 100 neighboring epithelial cells of the inferior turbinate mucosa, which we obtained during nasal operation to relieve nasal obstruction under general anesthesia, taking the utmost care not to injure the epithelium, in patients with allergic rhinitis before and after antigen challenge and in those with a deviated septum. The incidence of electron microscopic epithelial damage was significantly greater in patients with allergic rhinitis before antigen challenge than in those with a deviated septum, and in patients with allergic rhinitis 24 hours after antigen challenge compared to those before antigen challenge.¹¹ The cause of the diversity of opinions about the inward permeability of the nasal and tracheobronchial mucosa in patients with allergic rhinitis and bronchial asthma and their animal models

could not be determined in the present study, but it was considered to be due to differences in experimental conditions such as the degree of exudation in the airway mucosa, the degree of morphological changes in the airway epithelium, the density and amount of tracer used, and the sensitivity of the method in detecting changes in epithelial permeability. In the present study, nasal permeability to macromolecule did not show a significant difference from that of normal controls during the dominant exudative process in the nasal mucosa induced by intense antigen challenge on the nasal mucosa, but it was markedly enhanced after the dominant exudative process ceased. In clinical settings, it may be that epithelial permeability of the nasal mucosa to antigens such as mites and Japanese cedar pollen, which have almost the same molecular weight as HRP, is not different from that of normal controls during acute attacks of sneezing and rhinorrhea, but is enhanced markedly when intense acute nasal symptoms have subsided, triggering the next spell of hyperreactive nasal symptoms. This may also explain the mechanism of nonspecific hyperreactivity of the nasal mucosa to external stimuli.

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CLINICAL EVALUATION OF STAGING SYSTEM FOR NASOPHARYNGEAL CARCINOMA: COMPARISON OF FOURTH AND FIFTH EDITIONS OF UICC TNM CLASSIFICATION

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Staging nasopharyngeal carcinoma (NPC) by the UICC 4th-edition TNM classification system (the old system) did not give an accurate prognosis because of the uneven distribution of patients in each stage. This system was revised in 1997 (the new system). To evaluate the performance of the new system, 35 patients with NPC who had been staged by the old system were restaged according to the new system. Restaging of the patients resulted in an overall "downstaging." Differences in the overall survival rates of the early group (stages I, II, III), stage IVA, stage IVB, and stage IVC patients were statistically significant (75%, 48%, 74%, and 0%, respectively; $p = .01$). T4 was a significant factor of poor outcome (hazard rate, 2.932; 95% CI, 1.667 to 8.545), whereas N3 was not (hazard rate, 0.858; 95% CI, 0.281 to 2.618). The new staging system is more useful than the old system.

KEY WORDS — nasopharyngeal carcinoma, prognosis, TNM classification, UICC classification.

INTRODUCTION

Although nasopharyngeal carcinoma (NPC) occurs in the same anatomic location as head and neck carcinoma, several unique features of NPC in terms of etiology and pathology, such as its association with Epstein-Barr virus and the predominance of undifferentiated carcinoma, distinguish it from other head and neck carcinoma.^{1,2} The clinical aspects of NPC also have some differences. One major clinical feature is that NPC is associated with a higher incidence of regional and systemic metastasis than other head and neck carcinoma.³ Nevertheless, NPC was classified along with head and neck squamous cell carcinoma in the 4th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) staging guidelines⁴ (the old system), resulting in an uneven distribution of patients in each stage.^{5,6} According to those guidelines, up to 80% of patients present with stage III or IV.

The new staging classification (the 5th edition) was released by UICC in 1997.⁷ The purpose of this study was to clarify the difference between the old and new systems and to evaluate the performance of the new system in staging NPC.

PATIENTS AND METHODS

From January 1987 to January 1998, 35 patients received diagnoses of NPC and were treated in the Kanazawa University Hospital. The diagnosis of NPC was established by histologic examination. Ei-

ther computed tomography (CT) or magnetic resonance imaging (MRI) was performed on all patients. The patients were staged according to the old system (1987) at the initial diagnosis, and then were restaged according to the new system (1997) in March 1998. The differences in the systems are summarized in Table 1.^{4,7} Patients were basically treated with radiotherapy and adjuvant chemotherapy. Eight patients were treated with irradiation alone. Four patients were treated with irradiation alone because of poor general condition after radiotherapy, and 4 patients refused chemotherapy (stage IIA, 1; IIB, 1; III, 1; IVA, 2; IVB, 2; IVC, 1). The irradiation field was set from the skull base to bilateral supraclavicular lymph nodes (patients were irradiated with approximately 70 Gy to the primary NPC, 60 Gy to positive neck lymph nodes, and 45 Gy to negative lymph nodes). Cisplatin 100 mg/m² (1 day) and fluorouracil 750 mg/m² (5 days) were used for adjuvant chemotherapy. Six patients received 3 cycles, 12 patients received 2 cycles, and 7 patients received a single cycle of chemotherapy. Concurrent chemotherapy and radiotherapy was performed on 2 patients (stage IIB, 1; IVA, 1). Carboplatin (100 mg per patient) was administered once per week. Subsequent neck dissection was performed on 4 patients for residual cervical lymph node metastasis. The follow-up duration was calculated from the first examination day to either the date of death or December 31, 1998. The median follow-up period was 4.11 years. The overall survival rate was determined by the Kaplan-Meier method for each

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TABLE 1. OLD AND NEW TNM CLASSIFICATIONS OF NASOPHARYNGEAL CARCINOMA

Old Classification ⁴		New Classification ⁷
T1	Limited to 1 subsite	Limited to nasopharynx
T2	Invading 1 subsite	Invading oropharynx and/or nasal fossa
T2a		Without parapharyngeal extension
T2b		With parapharyngeal extension
T3	Invading oropharynx and/or nasal cavity	Invading bony structure and/or paranasal sinuses
T4	Invading skull and/or cranial nerves	Invading intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit
N0	No lymph node metastasis	No lymph node metastasis
N1	Single ipsilateral lymph node (<3 cm)	Ipsilateral lymph node metastasis (<6 cm)
N2		Bilateral lymph node metastasis (<6 cm)
N2a	Single ipsilateral lymph node (3-6 cm)	
N2b	Multiple ipsilateral lymph nodes (<6 cm)	
N2c	Bilateral or contralateral lymph nodes (<6 cm)	
N3	Lymph node metastasis (>6 cm)	Lymph node metastasis (>6 cm) or extension to supraclavicular fossa
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis
Stage I	T1N0M0	T1N0M0
Stage II	T2N0M0	
Stage IIA		T2aN0M0
Stage IIB		T1N1M0 or T2aN1M0 or T2bN0-1M0
Stage III	T3N0M0 or T1-3N1M0	T1-2N2M0 or T3N0-2M0
Stage IV	T4 (any N) or N2-N3 (any T) or M1 (any T, any N)	
Stage IVA		T4N0-2M0
Stage IVB		Any T, N3M0
Stage IVC		Any T, any N, M1

staging system. Kaplan-Meier plots of overall survival data were statistically analyzed by the log-rank method. Cox proportional hazard models were used to analyze the hazard rate, the 95% confidence interval (CI), and the p values of T and N classification for overall survival rates.

RESULTS

The distribution of the patients by the new and old systems is shown in Table 2.^{4,7} Restaging of the patients resulted in an overall "downstaging."

T Category. The number of T1 patients increased (14 cases in the new system and 10 cases in the old system), because the new system defines T1 as tumor confined to the nasopharynx. Therefore, invasion of more than 1 subsite, which was defined as T2 by the old system, was classified as T1 under the new system. The number of T3 patients decreased (3 in the new system and 5 in the old system), because the new system defines tumor invasion of the oropharynx and nasal cavity as T2a, and the old system defined this as T3. Consequently, the number of T2 patients (5 cases) did not change after restaging. The new system defines skull base invasion as T3, which had been classified as T4 by the old system, resulting in a decrease in the number of T4 patients (13 cases in the new system and 15 cases in the old

system). Table 3^{4,7} lists the differences between the old system and the new system. Many cases were also "downstaged" by T stage (from T2 to T1, 3 cases; from T3 to T2, 2 cases; and from T4 to T3, 2 cases). Only 1 case, with parapharyngeal space invasion, was "upstaged" (from T2 to T2b).

TABLE 2. COMPARISON OF DISTRIBUTION OF PATIENTS IN OLD AND NEW TNM CLASSIFICATIONS

	N0	N1	N2	N3	Total
Old system ⁴					
T1	2	0	4	4	10
T2	0	0	3	2	5
T3	1	0	3	1	5
T4	6	0	9	0	15
	9	0	19	7	35
New system ⁷					
T1	2	3	4	5	14
T2	1	2	1	1	5
T3	0	0	2	1	3
T4	6	0	7	0	13
	9	5	14	7	35
Stage	Old System		New System		
I	2		2		
II	0		6		
III	1		7		
IV	32		20		

TABLE 3. CHANGES IN DEFINITIONS OF T, N, AND STAGE FROM OLD SYSTEM⁴ TO NEW SYSTEM⁷

T category	
Downstaging	
Tumor invades >1 subsite of nasopharynx; T2→T1	
Tumor invades oropharynx and/or nasal cavity; T3→T2a	
Tumor invades cranial bone; T4→T3	
Upstaging	
Tumor invades bone except skull; T1, T2→T3	
Tumor invades parapharyngeal space; T1, T2→T2b	
Tumor invades infratemporal fossa, hypopharynx, or orbit; T1, T3→T4	
N category	
Downstaging	
Unilateral metastasis in lymph nodes measuring ≥3 cm; N2a→N1	
Unilateral metastasis in lymph nodes measuring ≤6 cm; N2b→N1	
Upstaging	
Extension to supraclavicular fossa; N1, N2c→N3	
Stage	
Downstaging	
Tumor invades oropharynx and/or nasal cavity; III→IIA	
N1; III, IV→IIB	
N2; IV→III	
Upstaging	
Tumor invades parapharyngeal space; I, II→III	
Tumor invades bone; I, II→III	

N Category. The number of N2 patients decreased (14 in the new system and 19 in the old system), because the new system defines N1 as metastasis to single or multiple ipsilateral lymph nodes measuring 3 to 6 cm in greatest dimension, whereas the old system defined N1 only as a single ipsilateral lymph node (<3 cm). Many cases were also "downstaged" by N stage (from N2a to N1, 1 case; and from N2b to N1, 8 cases; Table 3).

Stage. The number of patients with stage II carcinoma increased (6 in the new system and 0 in the old system), because N1 and tumor involvement of the oropharynx and nasal cavity were redefined as stage II. The number of patients with stage IV carcinoma decreased (20 in the new system and 32 in the old system), because N2 was reclassified to stage III. Nevertheless, 20 cases still belonged to stage IV.

Table 3 shows that many cases were also "downstaged" by "stage" (from stage III to IIA, 1 case; from III or IV to IIB, 6 cases; and from IV to III, 6 cases).

Survival of Patients. The overall survival data of patients by stage are plotted in the Figure.⁷ In the old system, stage IV had a 58% 5-year survival rate. Because the numbers of patients who belonged to stages I, II, and III were small, the patients were separated into early (stages I, II, III) and advanced (stage

IV) groups. The difference in overall survival rate between groups was not significant.

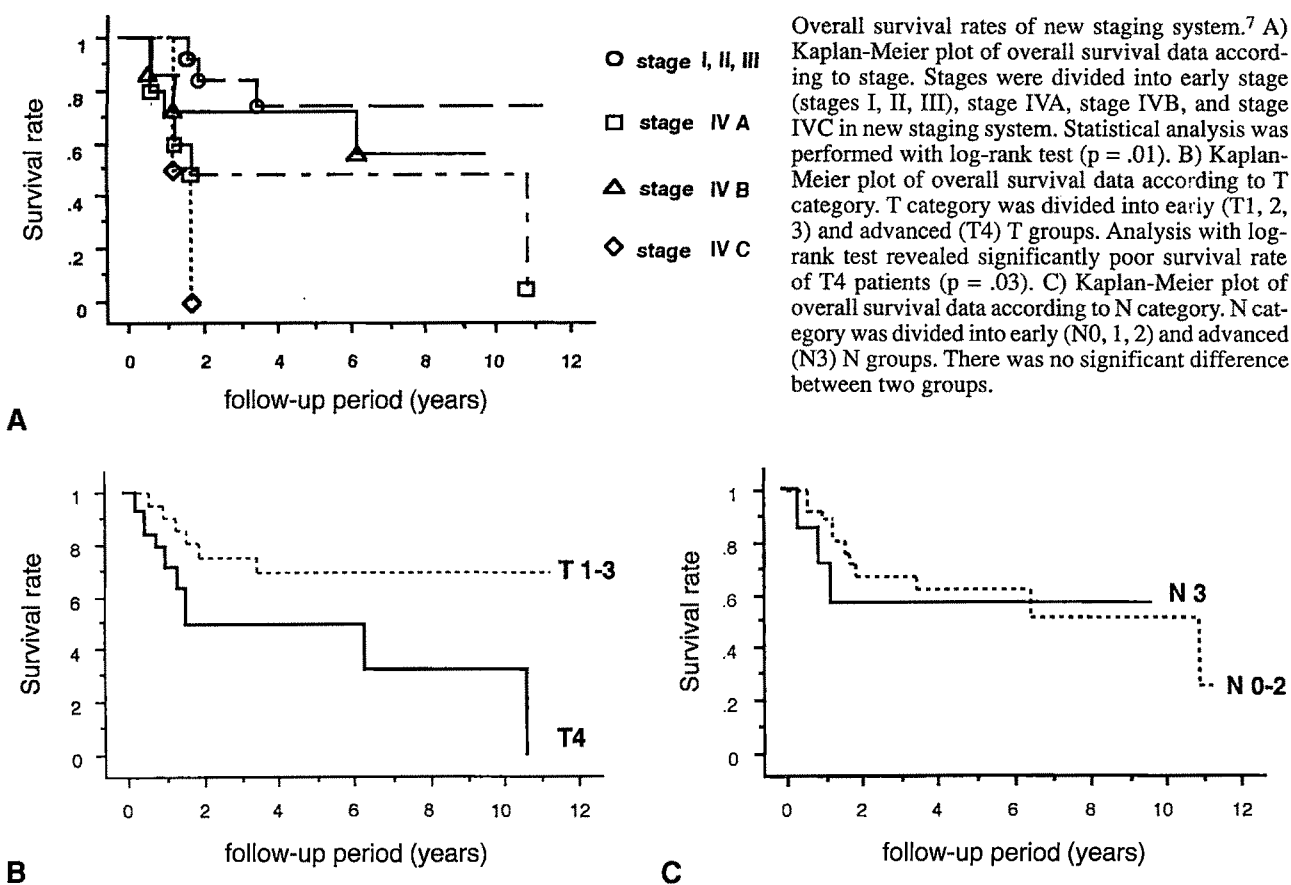
In the new staging system, stages I to III were again defined as early stage in this study (see Figure, A). The overall survival rates of the early stage, stage IVA, stage IVB, and stage IVC were 75%, 48%, 74%, and 0%, respectively ($p = .01$). However, the differences between the stages (I, IIA, IIB, III, IVA, IVB, IVC) were not significant. The number of patients with stage I and IIA was not sufficient for calculating a 5-year overall survival rate. The survival rates of stage IIB and stage III were 50% and 80%, respectively.

Based on the new system, the actuarial survival data of patients by T category and N category are plotted in the Figure, B,C. Patients with T4 disease had a significantly poorer prognosis than patients with T1 to T3 disease ($p = .03$; see Figure, B). The difference by N category was not significant ($p = .81$). In addition, there was no significant difference between N0 through N2 and N3 ($p = .85$; see Figure, C). T4 was a significant hazard in univariate analysis (hazard rate, 2.932; 95% CI, 1.667 to 8.545; $p = .0488$), whereas N3 was not a significant hazard ($p = .8917$; Table 4).

DISCUSSION

The disadvantage of the old system was that most patients with NPC were classified into stage IV,¹ perhaps because NPC was staged by the same scale as other head and neck carcinomas. Moreover, the presence of multiple cervical lymph node metastases was defined as stage IV. Actually, only 2 cases in our study fit in the category of stage I, whereas 32 cases were stage IV. Compared with other head and neck squamous cell carcinomas, NPC is a highly metastatic tumor.^{8,9} Therefore, the number of NPC patients with multiple cervical metastases is larger than that for other head and neck squamous cell carcinomas. On the other hand, NPC is more sensitive to chemotherapy and irradiation than other head and neck squamous cell carcinomas.^{1,8,10} Thus, bulky cervical lymph node metastasis sometimes disappears.

To improve the role of staging as a predictor of prognosis, the concept of Ho's system⁵ was adapted to the new system.¹¹ In the new system, all nasopharyngeal tumors confined within the nasopharynx were designated as T1. In the old system, these had been divided into T1 and T2. Teo et al¹² reported that the difference in overall survival rates of T1 and T2 in the old system was not statistically significant. Therefore, the idea of merging T1 and T2 in the new system seems to be reasonable. What was T4 in the old system was divided into T3 (skull base invasion) and T4 (intracranial invasion) in the new system. This



separation seems to have improved the performance of T4 as a predictor of poor prognosis (Table 1). In the new system, cervical lymph node metastasis was classified on the basis of the position of the lymph nodes, whereas in the old system it was based on the number and size of the lymph nodes.^{4,7}

Stage IV was divided into IVA, IVB, and IVC. Thus, the new system assigned patients to 7 uniform-sized stage groupings. The differences in survival rate among the early stage (stages I, II, III), stage IVA, stage IVB, and stage IVC were significant. Thus, division of stage IV into 3 subgroups is of value, in that each stage represents a different prognosis.

The T category in the new system seems functional, because patients staged below T3 in the new system had a better survival rate than those staged T4 in

TABLE 4. UNIVARIATE AND MULTIVARIATE REGRESSION ANALYSES OF T AND N PARAMETERS IN PREDICTING OVERALL SURVIVAL RATE

Variable	Hazard Rate	95% CI	p
Univariate			
T1-3 vs T4	2.932	1.667-8.545	.0488
N0-2 vs N3	0.858	0.281-2.618	.8917
Multivariate			
T1-3 vs T4	2.849	1.125-6.532	.0594
N0-2 vs N3	1.206	0.492-2.958	.7877

the new system. (The 5-year survival rates of stage IVA and stage IVB were 48% and 78%, respectively.) The major revision in the N category, which comes from the Ho system,⁵ is that the location, as well as the size, of the metastasized lymph nodes has been taken into account in the new system.^{5,7} Although this concept seems reasonable, the difference in N category did not reflect the outcome of the patients. In particular, N3 in the new system did not predict poor outcome in this study. Those patients whose neck nodes were not controlled by initial therapy could be rescued by neck dissection, whereas an uncontrolled primary tumor is hard to salvage. The poor prognosis of stage IVA, as compared to IVB, also suggests the prognostic significance of T4 rather than N3. It is generally accepted that NPC is a chemosensitive and radiosensitive tumor, which could be one of the reasons why bulky neck metastatic nodes were controlled by irradiation and adjuvant chemotherapy. Although primary nasopharyngeal tumors possess this favorable feature, this treatment often fails to eradicate advanced primary tumors. This finding could be attributable to anatomic reasons. It is difficult to deliver an adequate dose of irradiation to the primary tumor without risking damage to surrounding critical structures such as the brain stem, temporal lobe, and optic nerve.¹³ Patients with stage IIB had a worse prognosis than those with stage III. Patients with T2b

are included in stage IIB. Both patients with T2b, defined as parapharyngeal invasion, died in this study.¹⁴ These 2 patients had a large volume of tumor that occupied almost the entire parapharyngeal space. The posterior portion of the parapharyngeal space is located close to the temporal lobe. Therefore, the bulky parapharyngeal tumor might have been given an insufficient irradiation dose in an attempt to avoid damage to the temporal lobe.¹³ Although the number of T2 patients in this study is small, primary tumor volume may be a factor that affects prognosis.

Japan is not an endemic area of NPC. Therefore, the number of patients may not be sufficient to be statistically conclusive. Nevertheless, the new staging system predicts the outcome of patients more precisely than the old system. In order to improve the prognosis of T4 tumors, it is necessary to deliver an adequate dose to the primary tumor by means of new radiotherapy technologies such as conformal radiotherapy or intensity-modulated radiotherapy, which allow higher doses to the tumor while sparing surrounding normal tissues.

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COMPARISON OF 18-FLUORO-2-DEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY AND COMPUTED TOMOGRAPHY IN DETECTION OF CERVICAL LYMPH NODE METASTASES OF NASOPHARYNGEAL CARCINOMA

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Neck lymph nodes (LNs) from 18 patients with nasopharyngeal carcinoma (NPC) were evaluated with 18-fluoro-2-deoxyglucose positron emission tomography (FDG-PET). Eighteen NPC patients underwent head and neck FDG-PET and computed tomography (CT) for detection of suspected neck LN metastases. For final diagnosis, biopsies were taken from neck LNs with discordant findings between FDG-PET and CT. Meanwhile, standard uptake values (SUVs) of the FDG-PET images were calculated to differentiate metastatic LNs from benign LNs. A total of 90 neck LNs found on either FDG-PET or CT were evaluated. In addition to 27 concordant positive results and 42 concordant negative LN results, biopsy findings revealed 11 metastatic LNs that were detected by FDG-PET but not by CT. However, the SUVs of the 11 metastatic LNs and 7 benign LNs were not significantly different. The CT scanning showed positive findings for 1 metastatic LN with negative FDG-PET findings. In addition, the tumor stage was upgraded in 5 patients on the basis of FDG-PET findings. In comparison with CT, FDG-PET has a higher potential for detecting neck LN metastases of NPC and assessing NPC tumor stage.

KEY WORDS — computed tomography, 18-fluoro-2-deoxyglucose, nasopharyngeal carcinoma, positron emission tomography.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is very common in southern China, with an incidence of 10 to 30 people per 100,000 per year. It is distinct from other squamous cell tumors of the head and neck in that it shows aggressive infiltration locally and often has a high degree of regional spread at presentation, even though the primary tumor may have the appearance of a small or early lesion.^{1,2} There is clinical relevance for detecting metastatic lymph nodes (LNs), because the extent of the treatment is indicated by the presence or absence of metastatic LNs.

Imaging techniques such as computed tomography (CT) have improved staging of the neck as compared with clinical palpation. However, CT monitors cervical LN metastases by size and structural changes, not by metabolic activity; thus, the overall error rate of CT for assessing the presence or absence of cervical LN metastasis ranges from 7.5% to 28%.³ Consequently, there is a great need for an improved method that can accurately detect LN metastases in the neck,

particularly in a clinically negative neck. It is believed that alterations in metabolism precede structural alterations and that detection of metabolic alterations may improve diagnostic accuracy. 18-Fluoro-2-deoxyglucose positron emission tomography (FDG-PET) appears to be marginally better than CT for detecting cervical LN metastases. The uptake of 18-fluoro-2-deoxyglucose (FDG) in malignant head and neck tumors and metastatic cervical LNs was studied by Minn et al.⁴ Jabour et al.⁵ found that nonenlarged LNs negative for metastatic disease on CT scanning were detected on FDG-PET images. However, FDG-PET scanning of cervical LN metastases of NPC is still in its infancy. We aimed in this study to investigate the usefulness of FDG-PET in the identification of cervical LN metastases of NPC, according to histopathologic findings and in comparison with CT results.

PATIENTS AND METHODS

Patients. Eighteen NPC patients (5 women and 13 men, ages 20 to 66 years) underwent head and neck

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PATIENT DATA

Case No.	Sex	Age (y)	Positive Neck Lymph Nodes					
			FDG-PET			Computed Tomography		
			No.	TNM	Stage	No.	TNM	Stage
1	M	20	3	T1N2M0	III	2	T1N2M0	III
2	M	29	2	T2N2M0	III	1	T2N1M0	III
3	M	35	3	T2N2M0	III*	1	T2N1M0	IIB
4	F	38	2	T1N2M0	III	3	T1N2M0	III
5	F	40	3	T1N2M0	III	2	T1N2M0	III
6	M	42	3	T1N2M0	III*	1	T1N1M0	IIB
7	F	45	2	T1N1M0	IIB	1	T1N1M0	IIB
8	M	48	1	T1N1M0	IIB	2	T1N1M0	IIB
9	M	49	3	T1N2M0	III	2	T1N2M0	III
10	M	53	4	T2N2M0	III	2	T2N2M0	III
11	M	56	3	T1N2M0	III*	1	T1N1M0	IIB
12	F	57	2	T1N1M0	IIB	1	T1N1M0	IIB
13	F	58	4	T1N2M0	III*	1	T1N1M0	IIB
14	M	58	2	T1N1M0	IIB	3	T1N1M0	IIB
15	M	60	2	T2N1M0	IIB	2	T2N1M0	IIB
16	M	63	1	T1N1M0	IIB	1	T1N1M0	IIB
17	M	65	2	T1N2M0	III	2	T1N2M0	IIB
18	F	66	3	T2N2M0	III*	2	T2N1M0	IIB

*Tumor stage upgrade based on 18-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) findings.

FDG-PET and CT imaging for detection of suspected neck LN metastases (see Table). None of the 18 patients had undergone surgery, radiotherapy, or chemotherapy. The FDG-PET and CT studies were performed within a 1-week period. After the positron emission tomography (PET) and CT studies, biopsy specimens were taken only from neck LNs that yielded discordant findings on FDG-PET versus CT. There were no diabetic patients in our series.

FDG-PET Imaging. The patients fasted overnight before the FDG-PET study. No patient in this study was found to have a glucose level higher than 120 g/dL. The FDG-PET imaging was performed with a GE advance PET scanner (GE Medical Systems, Milwaukee, Wis). The GE advance PET scanner produces 4.25-mm-thick image planes (18 direct planes and 17 cross planes). The axial field of view was 15 cm, and the FWHM (full width of half maximum) was 5 mm. Each patient was positioned such that the head and neck were inside the scanner, allowing the regions of interest (ROIs) to be drawn in the center of the field of view. The landmarks for positioning were determined from the CT scans. Transmission scans using a rotating germanium 68 pin source were performed on all patients before injection of FDG. Transmission images were reconstructed with filtered back-projection and smoothed with a 7.0-mm-wide Hann window. Then, emission imaging began 30 minutes after intravenous injection of 370 Mbq (10 mCi) of FDG. Emission images of the head and neck were acquired for 20 minutes, and approximately 1 million counts per plane were obtained. Emission im-

ages were reconstructed by the filtered back-projection method using a 5.0-mm-wide Hann window. The emission data were corrected for scatter, random events, and dead time. The image pixel size was 3.0 mm in a 128 × 128 array. The FDG-PET images were analyzed both qualitatively and quantitatively as follows. The transverse PET images were individually reoriented into transverse planes to obtain better-corresponding views of the cervical LNs to compare with CT findings. The FDG-PET images were visually interpreted by 2 experienced nuclear medicine physicians without prior knowledge of CT findings or final histopathologic confirmation. Any visually positive hot spot on FDG-PET was considered to be a metastatic LN (Fig 1).⁶ The ROIs were drawn over the focal abnormality on the FDG-PET images of patients with final histopathologic confirmation of discordant neck LNs. After correction for radioactive decay, the ROIs were analyzed by computing standard uptake values (SUVs): mean ROI radioactivity (in millicuries per milliliter) divided by the injected dose (in millicuries per gram of body weight).⁷

CT Imaging. The CT scanning was performed in the transverse and coronal planes after the intravenous injection of contrast medium. The CT scans were obtained with a Somatom DRH CT scanner from Siemens (Erlangen, Germany) with an axial section thickness of 5 mm from the skull base to the manubrium. The CT images were assessed by 2 experienced radiologists who had no knowledge of the FDG-PET or histopathologic findings. The diagnosis of neck LN malignancy was made according to the follow-

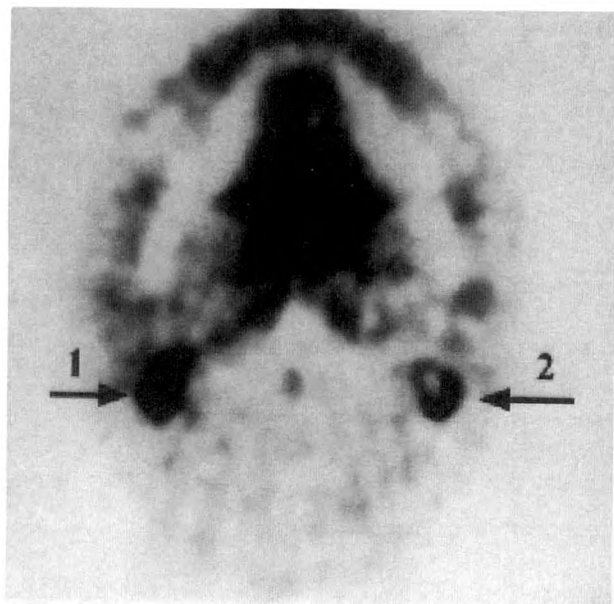


Fig 1. Positive 18-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) image (transverse section). On opposite sides of neck, 2 lymph nodes have significant FDG uptake (arrows 1 and 2).

ing previously established morphological criteria (Fig 2)⁸: 1) neck LNs with a greatest dimension of ≥ 10 mm; 2) LNs of any size with central necrosis; or 3) LNs of any size with a contrast-enhancing rim with or without central necrosis.

RESULTS

A total of 90 neck LNs on either FDG-PET or CT were found and evaluated (see Table). Among them,

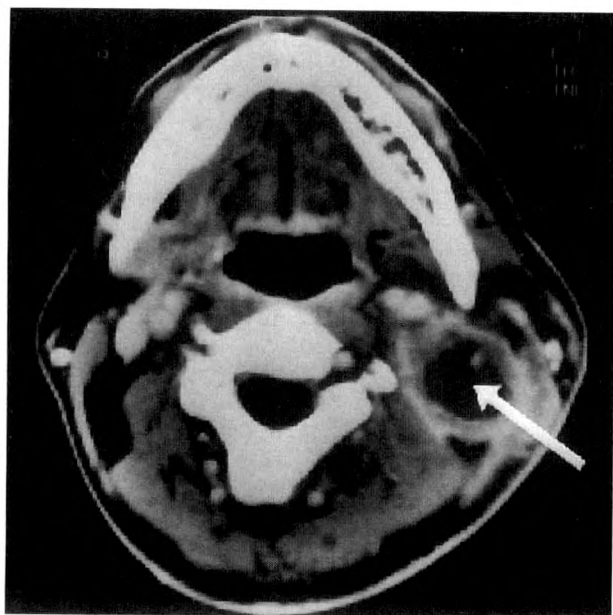


Fig 2. Positive computed tomographic image (transverse section). On left side of neck, lymph node has greatest dimension of ≥ 10 mm, central necrosis, and enhancing rim with central necrosis (arrow).

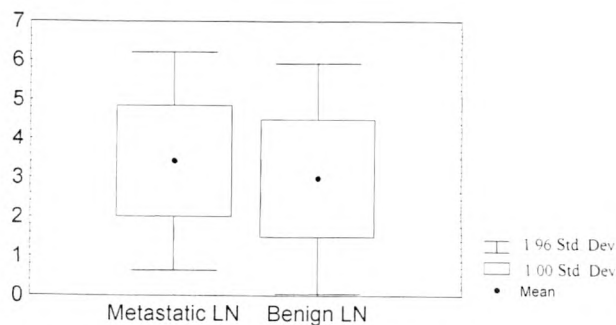


Fig 3. Standard uptake values of metastatic and benign lymph nodes (LN) from FDG-PET.

69 had concordant findings, including 27 positive LNs and 42 negative LNs on both FDG-PET and CT. In the remaining 21 discordant LNs, 18 had positive FDG-PET findings but negative CT findings, and 3 had positive CT findings but negative FDG-PET findings. The biopsy results from the 18 discordant LNs with positive FDG-PET findings but negative CT findings revealed 11 metastatic LNs and 7 benign LNs. The SUVs from FDG-PET scans of the 11 metastatic LNs (1.3 to 5.2, 3.4 ± 1.4) and 7 benign LNs (0.8 to 5.0, 3.0 ± 1.5) were not significantly different (Mann-Whitney U test, $p = .594$; Fig 3). The biopsy results from the 3 discordant LNs with positive CT findings but negative FDG-PET findings revealed 1 metastatic LN and 2 benign LNs. In addition, the tumor stage was upgraded in 5 patients on the basis of FDG-PET findings (see Table).

DISCUSSION

Since the 1930s, it has been known that cancer cells have higher glycolytic rates than normal cells.⁹ The glucose analog FDG is metabolized in normal and neoplastic tissue in proportion to the rate of tissue glucose metabolism.¹⁰ The FDG is metabolically trapped in the intracellular space — more so in cancers than in normal tissues¹¹ — and can be used to identify tumors on the basis of accelerated glycolytic rates on PET. Because of the higher glycolytic rate of many neoplasms compared with normal tissue, FDG-PET is now being applied to many organ systems for cancer identification.¹¹ Several authors have described the uptake of FDG in cervical LN metastases.^{5,12} However, FDG-PET has been shown by Greven et al¹³ to be limited in the detection of cervical LN metastases, similar to the initial experiences of Jabour et al⁵ and Bailet et al.¹⁴ However, no studies have been done on NPC, which is very common in the Chinese population. In this study, our purpose was to evaluate the diagnostic potential of FDG-PET for the detection of cervical LN metastases in NPC in comparison with conventional CT imaging.

A major problem with the CT radiologic criteria is that when LNs show no contrast enhancement or

central necrosis on CT, they are considered metastases on the major criterion of size.^{3,8} One centimeter is considered the critical size for differentiation between metastatic and benign LNs. As a consequence, the specificity of this technique is increased, but at the expense of sensitivity, because smaller LNs with no contrast enhancement or central necrosis are excluded by definition. In our study, 11 cervical LNs not detected by CT but positive on FDG-PET were proven to be metastatic by histopathologic analysis. In addition, the tumor stage was upgraded in 5 patients on the basis of FDG-PET findings (see Table). In a review of the literature, we found that Jabour et al⁵ and Braams et al⁶ investigated patients with oral cancers and found nonenlarged, positive LNs on FDG-PET that were negative on CT — similar to our results.

The biopsy results revealed 1 discordant metastatic LN with a positive CT finding that was not detected by FDG-PET. The failure of FDG-PET to detect that metastatic LN may be attributed to low glycolytic activity of the metastatic lesion.¹⁵⁻¹⁷ Another possible explanation for the failure of FDG-PET to detect that metastatic LN is that FDG uptake is likely proportional to the number of viable tumor cells and

their metabolic activity. Thus, a small number of cells in microscopic nodal deposits virtually ensures false-negative results.¹⁸ Another major problem with FDG-PET is the differentiation between benign and metastatic LNs. In this study, 7 false-positive findings on FDG-PET were probably due to the accumulation of FDG in metabolically hyperactive but pathologically benign LNs.^{5,15} Unfortunately, there were no differences in SUVs between benign and metastatic LNs; thus, the SUVs provided no additional information. Similar results were found in the oral cancer study by Braams et al.⁶

According to the procedure guideline for tumor imaging using FDG of the Society of Nuclear Medicine and from a literature review of studies¹⁹⁻²¹ that used FDG-PET to examine head and neck cancers, the practice of beginning emission imaging after an FDG uptake period of 30 minutes, as in this study, is both adequate and time-saving for clinical practice.

Although no sole anatomic or physiological study, including FDG-PET, is completely accurate for detecting cervical LN metastases, we think that FDG-PET, with its higher sensitivity, should be considered a better tool than CT for detecting LN metastases and assessing the tumor stage of NPC.

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MORPHOLOGY OF THE HUMAN THYROGLOSSAL TRACT: A HISTOLOGIC AND MACROSCOPIC STUDY IN INFANTS AND CHILDREN

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The anatomic development of thyroglossal tract remnants is not understood at present. For analysis of morphology and growth patterns of thyroglossal tract remnants, we used histologic whole organ serial sections to determine developmental changes through the first years of life. Larynges of 58 infants and children ages 1 month to 13 years were obtained in whole organ serial step-sections in an axial plane. The slides were stained with hematoxylin and eosin, Alcian blue, and periodic acid-Schiff stains. Altogether, 3,247 histologic slices were examined. The resulting data were then correlated with the age and sex of the specimens. We found, in 24 cases (41.3%), remnants of the thyroglossal tract or ectopic thyroid tissue. In 4 specimens (16.6%), a complete thyroglossal tract could be observed that presented a ventral path in relation to the hyoid bone with no contact with the perichondrium of the cartilage. Hormonal activity of ectopic thyroid tissue was proven in 20 cases (34.5%). Thyroid follicles were located in 2 cases (3.5%) in the hyoid bone. The thyroglossal ducts revealed a modest tendency for a left-sided pathway, whereas thyroid follicles were located more on the right paramedian side. Morphometric data on the development and structure of the thyroglossal tract and the thyroid follicles during infancy and childhood are presented. The study provides quantitative data of clinical interest that elucidate the anatomy of thyroglossal tract remnants. In addition, our investigation supports Sistrunk's operative approach for avoiding recurrences in the treatment of thyroglossal duct cysts.

KEY WORDS — anatomy, hyoid bone, Sistrunk procedure, thyroglossal duct cyst, thyroglossal tract.

INTRODUCTION

Thyroglossal duct cysts (TDCs) are embryological remnants of the thyroglossal tract. The successful treatment of TDCs is predicated on a solid understanding of the embryology of thyroid gland and hyoid bone anatomy and the developmental changes that occur in this area during the first years of life.

During the fourth week, the human embryo develops a group of 5 paired arches at the cranium. These are the branchial arches, soon completed by the formation of 4 ectoderm invaginations, or branchial clefts, and 4 endoderm branchial pouches. These primary organs will mostly disappear, with the remainder forming the postfetal head and neck structures. The thyroid gland originates at the foramen cecum and descends anterior to the pharynx to its final position close to the larynx.¹ This pathway is divided by the hyoid bone into upper and lower segments during the second gestational month. A failure of the obliterative process of the thyroglossal tract, or retained epithelial cysts, builds the basis for the origin of TDCs.² Knowledge of the path taken by the thy-

roglossal tract, particularly in relation to the hyoid bone, remains the most crucial factor in determining optimum treatment of TDCs.

Although extensive descriptive data regarding the operative treatment^{3,4} and the pathology of surgical specimens of TDCs are available today,⁵ only limited and contradictory information about the anatomic course of the thyroglossal tract in relation to the hyoid bone is found in the literature.⁵⁻⁷ Thus far, few cases have been reported in which the TDC penetrates into the hyoid bone.⁸ This pathological phenomenon is not currently understood. The penetration of the hyoid bone by the thyroglossal tract may be the result of forward growth of the hyoid bone after development of a TDC ventral to the hyoid bone.⁹

No studies of thyroglossal duct remnants in serially step-sectioned larynges from the first 13 years of life or data regarding the incidence of remnants in an otherwise healthy examination group are available.

The purpose of this study was to analyze the anatomic course of the thyroglossal tract on histologic

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No. of cases

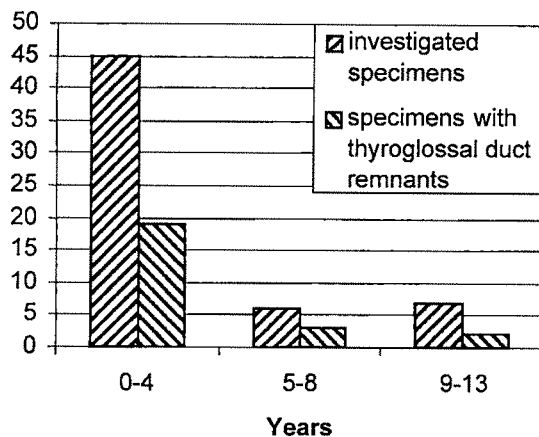


Fig 1. Age distribution among 58 investigated specimens.

sections from a pediatric population. Special interest was paid to the hormonal activity of thyroglossal tract remnants and the topographic relationship between the thyroglossal tract and the perichondrium of the hyoid bone. These anatomic data are presented to illuminate the complex nature of thyroglossal duct disease and to demonstrate the possible reasons for failure after inadequate surgical procedures.

METHODS

The data for this study were obtained from a group of autopsy specimens from 58 infants and children at the Institute of Forensic Medicine of the University of Cologne. The larynges and the hyoid bones were removed at routine autopsy 12 to 64 hours after death. If tumors or traumatic lesions of the neck region became evident during autopsy, these specimens were excluded from further investigation. Thirty of the deceased were male and 28 were female. The mean age of the 30 male subjects was 30 months (range, 5 weeks to 12.5 years), and the mean age of the 28 female subjects was 21.5 months (range, 2 months to 13 years). Figure 1 presents the age distribution of the 58 examined specimens.

During autopsy, the larynx was removed in continuity with the lung, trachea, thyroid gland, tongue, and skin covering the hyoid bone. Before histologic examination, the lung and trachea were transected between the fifth and sixth tracheal rings. The remaining specimen contained the larynx with the attached hyoid bone, the 6 most cranial tracheal rings, the thyroid gland, and the tongue.

The specimens were submitted to 10% formalin fixation. Decalcification was performed in 2% ethylene diamine tetraacetate. After dehydration in alcohol-acetone, the specimens were embedded in paraffin. Serial sections were made of each paraffin block. Altogether, 3,247 histologic slices were examined.

The thickness of the sections was 8 μ m. The distance between slices was 50 μ m. The slices were stained with hematoxylin-eosin and Alcian blue. For analysis of the hormonal activity of thyroid cysts, we applied periodic acid-Schiff stain. Each specimen in which remnants of the thyroglossal tract or the thyroid gland could be found was documented with a reflex camera (Olympus OM 4) connected to a microscope (Olympus BX 50) at different magnifications.

RESULTS

Among the 58 specimens of infants and children, we found 24 cases (41.3%) exhibiting remnants of the thyroglossal tract or ectopic thyroid tissue. Among this group, we found a modest male prevalence of 54.2%. Our results yield further clarification on the topographic course, the histologic epithelial patterns, and the hormonal activity of the thyroglossal tract system and will be addressed point by point.

Topographic Course and Localization of Thyroglossal Tract. We observed, in 4 specimens (16.6%), a complete thyroglossal tract extending from the top of the thyroid gland to the base of the foramen cecum. The course of this tract remained ventral to the hyoid bone in all section planes. The duct was noted to lie in the median plane in 2 specimens, and in the paramedian plane on the left side in the remaining 2 specimens. In all 4 specimens, thyroid cysts could be noted in close proximity to the thyroglossal tract. Three specimens showed a division of the tract system into 3 or more ducts. In 1 case, we noticed that the duct ended blind on the ventral side of the hyoid bone perichondrium.

Topographic Course and Localization of Thyroid Cysts. In addition to the aforementioned 4 specimens with thyroglossal tracts and ectopic thyroid tissue, we found thyroid follicles alone in 20 specimens (34.5%). In 11 cases (55%), the thyroid follicles were located ventral to the hyoid bone, in 3 specimens (15%), dorsal, and in 6 cases, a combination of ventral and dorsal (30%). In 9 of the 20 cases (45%), we found the ventrally located thyroid follicles in a median plane in relation to the hyoid bone. In 6 specimens, the cysts were observed on the right, and in 2 cases, on the left paramedian side. Three thyroid follicles were noted to lie in the paramedian plane dorsal to the hyoid bone: 1 on the left, and 2 on the right side.

Histologic Epithelial Patterns of Thyroglossal Tracts and Ectopic Thyroid Tissue. The epithelial lining of the ducts was primarily stratified columnar, with slightly less stratified cuboid lining. Some section planes exhibited stratified squamous epithelium.

AGE AND SEX OF SUBJECTS AND FREQUENCY OF THYROGLOSSAL DUCT REMNANTS (N = 58)

Age (y)	Sex		Thyroglossal Tract		Ectopic Thyroid Tissue				Hormonally Active Tissue
	Male	Female	Median	Paramedian	Ventral	Dorsal	Median	Paramedian	
Less than 1	17	15	2	1	9	2	6	3	11
1-4	6	7	0	1	1	2	4	3	3
5-8	3	3	0	0	2	1	1	2	2
9-13	4	3	0	0	2	0	1	0	3
Overall	30	28	2	2	17	5	12	8	20

This pattern was interpreted as the artificial result of a vertical cut through the stratified cuboid epithelium.

The epithelial lining of the thyroid cysts was single cuboid in 22 of 24 cases. In 2 specimens, we noted a transition from columnar to flat epithelium. Most of the thyroid cysts were covered by a connective tissue sheet. The number of cysts varied considerably. Most thyroid cysts were found dorsal to the hyoid bone.

Hormonal Activity of Ectopic Thyroid Tissue. The hormonal activity of the thyroid cysts was assessed with the periodic acid–Schiff reaction. Mucus, found in the lumen in contact with the epithelium, was pres-

ent in 20 of 24 specimens that had ectopic thyroid tissue in addition to thyroglossal ducts (83.3%).

In all specimens, we found the thyroglossal duct ventral to the hyoid bone, with no contact with the perichondrium of the cartilage. However, the thyroid follicles were often closely attached to perichondrium. Only 2 extraordinary cases were observed in which the follicles came to lie in the body of the hyoid bone. Likewise, in all cases of thyroid tissue lying dorsal to the hyoid bone, we found connective tissue surrounding the follicles.

Findings concerning the age and sex of the subjects and the frequency of thyroglossal duct remnants are summarized in the Table. The most instructive

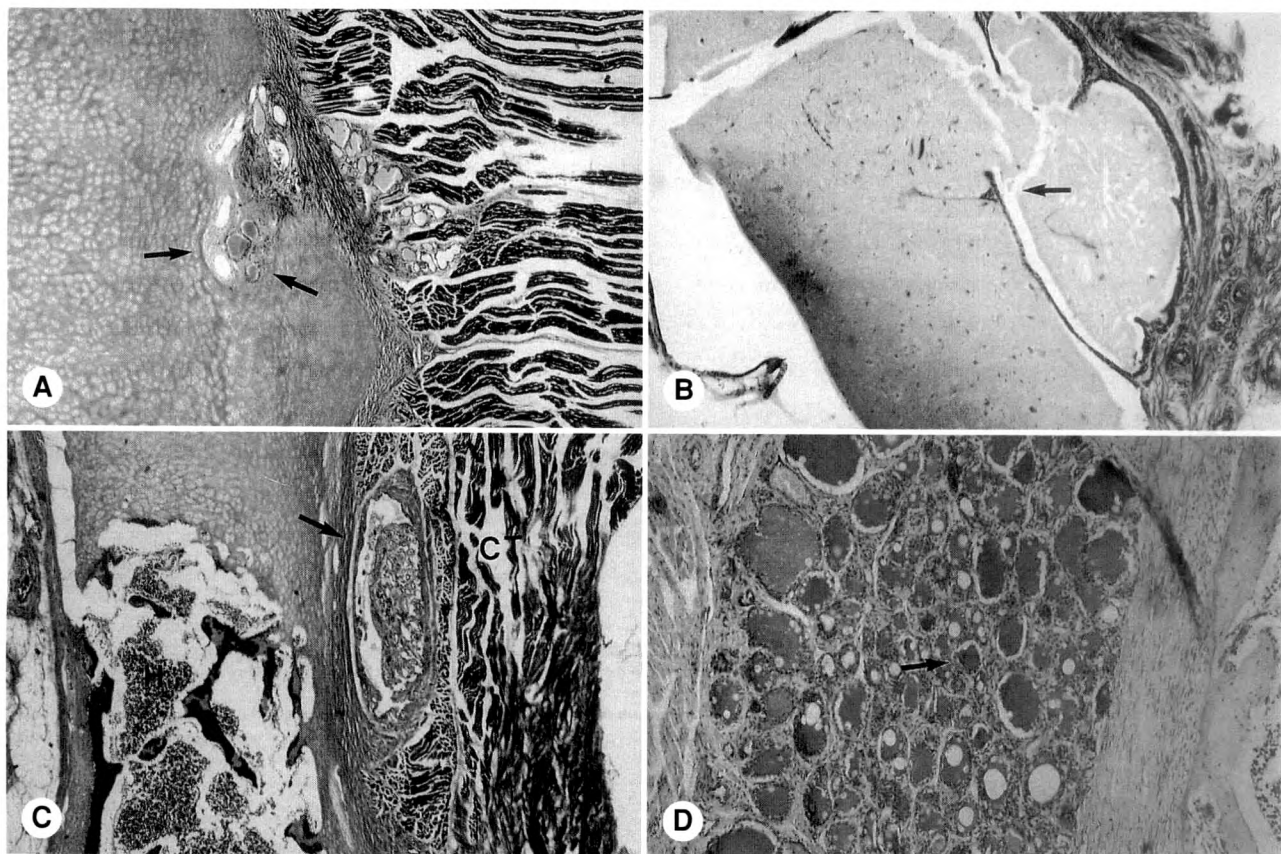


Fig 2. Representative histologic findings. A) Thyroid follicles (arrows) and ductuli located in cartilage of (nonossified) hyoid bone of 11-month-old child (Goldner stain, original $\times 25$). B) Thyroglossal duct with connective tissue septum (arrow) of 5-month-old child (Goldner stain, original $\times 75$). C) Thyroglossal duct located ventral to hyoid bone (H) of 7-year-old child (Goldner stain, original $\times 25$). Arrow shows thyroid follicles lying in connective tissue (CT). D) Periodic acid–Schiff–positive stained thyroid follicles (arrow) indicate hormonal activity of tissue of 8-month-old child (original $\times 52$).

histologic findings are presented in Fig 2.

DISCUSSION

The TDC is the most common congenital cyst found in healthy young adults and often occurs as a painless swelling in the midline of the neck.¹⁰ A midline fluctuating mass, dysphagia, infected fistulas, mid-neck tenderness, and cough are the more prominent symptoms that lead the physician to a diagnosis. Although TDCs are often present in childhood, they can also afflict the adult population.³

In 1893, Schlange¹¹ was the first to advocate excision of the central portion of the hyoid bone for surgical treatment of TDCs. However, Sistrunk,¹² who described this procedure extensively in 1920, is regarded as the founder of this operative technique, which continues to remain the most effective treatment of TDCs. Nonetheless, inadequate excisions and troublesome recurrences still are encountered, with well-documented return rates for TDC operations.¹³ Recurrence rates vary widely, from 8% to 40%. Simple cystectomy without hyoidectomy and preexisting infection are the leading causes of TDC reappearance.¹⁴ Dissecting the thyroglossal tract without removing it as a total block may lead to remnants of thyroid follicles. In our investigation, these follicles existed in all cases in combination with thyroglossal ducts and could be identified singularly in 34.5%. The basics of Sistrunk's technique should include the removal of the cyst and the body of the hyoid bone, and the excision of a core of the suprahyoid portion of the tract to the foramen cecum.¹² In 1992, Horisawa et al¹⁵ studied the optimum depth for core-outs toward the foramen cecum. They proposed that 10 to 15 mm of the hyoid bone should be removed and that the depth of the core-out should be less than 5 mm in young children to avoid the breakdown of

branched ductuli near the foramen cecum.¹⁵ It is confusing that despite the supporting literature, the treatment of TDCs is often mismanaged.⁴

The crucial point in understanding Sistrunk's rationale is knowledge of the embryogenesis of the tongue, the thyroid gland, and the hyoid bone. The path of the thyroglossal tract is intimately related to the hyoid bone. Despite Sistrunk's distinct exploration, there is uncertainty concerning the exact path taken by the thyroglossal tract, particularly in relationship to the hyoid bone. Sistrunk,¹² Ward et al,¹⁶ and Telander and Deane¹ suggest that the course of the thyroglossal duct comes to lie ventrally or dorsally to, or along a path through, the hyoid bone. Brintnall et al¹⁷ and Ellis and van Nostrand⁶ support the thesis that the course of the thyroglossal duct is either ventral to or through the hyoid bone. On the basis of our data, we believe that the thyroglossal tract runs ventral to the hyoid bone in close relationship to the perichondrium of the hyoid bone. We found no evidence that the bone develops around the tract, thus entrapping it.

CONCLUSIONS

This study supplies detailed data on the anatomy of thyroglossal ducts and thyroid follicles in infants and children. It is the first to use serially step-sectioned histologic specimens from a pathologically inconspicuous examination group for the investigation of thyroglossal tract remnants.

We conclude that the classic Sistrunk procedure should be the treatment of choice for the management of TDCs to minimize the risk of recurrence. Dissecting the thyroglossal tract without excision as a total block may lead to remnants of thyroid follicles and would thus require further surgical intervention.

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LASER PARTIAL EPIGLOTTIDECTOMY AS A TREATMENT FOR OBSTRUCTIVE SLEEP APNEA AND LARYNGOMALACIA

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Obstructive sleep apnea (OSA) and laryngomalacia are two different entities. Occasionally, they may have a common etiology: an elongated, flaccid, and lax epiglottis that is displaced posteriorly during inspiration causing airway obstruction. Twenty-seven adults with a diagnosis of airway obstruction or OSA of various degrees, and 12 infants with severe stridor associated with frequent apneas due to laryngomalacia, who on fiberoptic examination were found to have a posteriorly displaced epiglottis, underwent partial epiglottidectomy with a CO₂ laser. Their postoperative recovery was uneventful. Polysomnographic studies performed after operation in the adult patients demonstrated statistically significant improvement in 85% of the patients. In all the cases of laryngomalacia, stridor ceased permanently after surgery, together with complete cessation of the apneic episodes. This study demonstrates that similar pathophysiological mechanisms may be involved in both laryngomalacia and in OSA. Effective and relatively safe treatment can be achieved by partial resection of the epiglottis with a microlaryngoscopic CO₂ laser.

KEY WORDS — carbon dioxide laser surgery, epiglottis, laryngomalacia, sleep apnea syndrome.

INTRODUCTION

Obstructive sleep apnea (OSA) syndrome is a complex and widespread disorder with a large variety of subjective symptoms and associated objective medical problems. It is characterized by periodic cessation of breathing during sleep that is caused by the collapse of upper airway structures at various levels.¹ Associated medical conditions may include cardiac and pulmonary hypertension with resultant cor pulmonale, cardiac arrhythmia, chronic obstructive pulmonary disease, increased risk of cardiovascular morbidity and mortality, and cognitive and personality problems.² Given the potentially serious consequences of OSA, Phillipson³ referred to this syndrome as “a major public health problem.” Physicians in a wide variety of medical disciplines are involved in the diagnosis and treatment of patients suffering from this syndrome. Surgery is indicated for patients who have an underlying specific, surgically correctable abnormality that causes the OSA or for whom other noninvasive treatments have been unsuccessful or rejected by the patient. The surgical treatment of OSA has evolved from crude but effective techniques such as tracheotomy to a variety of site-specific procedures, described in the last 2 decades, directed at the collapsible areas of the upper airway.

A successful surgical result can be expected only if the site(s) of obstruction is correctly identified.⁴

Unfortunately, the overall success rate of surgical techniques such as nasal reconstruction or pharyngeal surgery does not exceed 50%.² With more complex techniques, such as mandibular osteotomy, midline glossectomy, hyomandibulopexy, and mandibular or maxillary advancement, the success rate may reach 70% to 80%, but some of these procedures are associated with a high morbidity rate.²

Laryngomalacia is the most common laryngeal anomaly in infants and children.⁵ It involves the collapse of redundant supraglottic tissues into the laryngeal inlet during inspiration.⁶ One of the anatomic abnormalities seen in laryngomalacia is an unusually long and flaccid epiglottis that is displaced posteriorly against the posterior pharyngeal wall during inspiration.^{7,8} Other abnormalities seen are short aryepiglottic folds and bulky arytenoids that prolapse anteriorly on inspiration.⁷ In extreme cases, the epiglottis may be even “sucked down” through the glottis to such a degree that total airway obstruction may occur.^{9,10} The use of the flexible fiberoptic endoscope permits direct examination of the larynx, allowing us to confirm the diagnosis of laryngomalacia as early

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as the first day of life.¹¹ Although laryngomalacia is usually a self-limiting condition that resolves by the age of 2 years, occasionally it may persist into later childhood, causing inspiratory obstruction.¹² Some authors have reported "acquired laryngomalacia," even in elderly patients.¹³⁻¹⁸

The majority of infants with laryngomalacia can be managed expectantly in the knowledge that with growth and maturity, the laxity of the supraglottic tissues will decrease.⁶ Until then, supportive management, close follow-up, and parental reassurance are the only treatment needed. Although, in most cases, laryngomalacia takes this benign course, occasionally it can be so severe that it may cause respiratory and feeding problems that interfere with normal growth and development.¹⁹ In extreme cases, it may even be the cause of sudden infant death syndrome.²⁰⁻²² The incidence of severe cases of laryngomalacia varies from 10% to 15%.^{5,23-25} In life-threatening cases, surgical treatment is indicated.²⁶ In the past, the only method used to treat severe cases of laryngomalacia was tracheotomy.^{8,24} However, infant tracheotomy carries a significant risk of morbidity and mortality, with gross disruption of family life. In 1922, Iglauer²⁷ pioneered the surgical treatment of laryngomalacia by removing the epiglottic tip using a nasal snare. In 1944, Schwartz²⁸ removed a V-shaped wedge from the epiglottis of a child with laryngomalacia. More recently, an endoscopic approach using the surgical CO₂ laser has been used to deal with these cases.^{24,29} The CO₂ laser has been used in microlaryngeal surgery since the early 1970s, and Vaughan³⁰ first described endoscopic CO₂ laser epiglottidectomy in 1978. Since then, the use of the CO₂ laser in different microlaryngeal procedures has become a common practice in many medical centers.

Laryngeal obstruction has been reported to contribute to both adult OSA and apnea of infancy⁴; however, it has not been commonly recognized clinically. Recently, the similarity between the symptoms and signs of laryngomalacia and OSA drew the attention of several authors to the possibility that an abnormally long, lax, and/or flaccid epiglottis might be one of the causes not only of laryngomalacia, but also some cases of OSA.^{15-17,31-33} In the cases reported by these authors, laryngeal obstruction and OSA were caused by the epiglottis, which was tilted backward against the posterior wall of the hypopharynx. During inspiration, it was actually sucked downward until total obstruction of the laryngeal inlet occurred. The diagnosis of this disorder was made possible by direct visualization of the epiglottis during sleep and while the patient was awake by means of the flexible fiberoptic endoscope.

Catalfumo et al³¹ and Woo¹⁵ treated this disorder with CO₂ laser epiglottidectomy. By trimming the upper half of the suprahoid epiglottis, they alleviated airflow-induced epiglottis prolapse.

The purpose of this study was to demonstrate that in both infants with laryngomalacia and adults with OSA, a contributing factor might be a flaccid and lax epiglottis that, on inspiration, prolapses backward and downward, causing airway obstruction. We would like to emphasize the role of fiberoptic laryngoscopy in the evaluation and workup of these patients, and to demonstrate that the obstruction can be relatively easily alleviated by resection of the upper part of the epiglottis with the CO₂ laser.

PATIENTS AND METHODS

Study Subjects. Four hundred seventy-two patients were referred to the Department of Otolaryngology-Head and Neck Surgery at Rambam Medical Center from several sleep research laboratories during the years 1991 through 1997 for examination and evaluation after a nocturnal polysomnographic study. In all of these patients, OSA syndrome of various degrees was diagnosed. A thorough otorhinolaryngological examination was performed, including direct fiberoptic nasopharyngolaryngoscopy, which was performed while the patients were awake and, in 187 patients, also during night sleep (Richards-Wolf flexible nasopharyngolaryngoscope, 3.5 mm). Videotape recordings were made and reviewed later before surgery was planned.

Twenty-seven patients were found to have narrowing to various degrees of the laryngeal inlet due to an abnormal epiglottis or its abnormal backward displacement against the posterior pharyngeal wall according to the rating scale proposed by Catalfumo et al.³¹ This group comprised 21 men and 6 women (male/female ratio, 3.5/1) ranging in age from 19 to 68 years (mean, 42 ± 12.4 years). The mean body mass index (BMI) of the patients was 23.4 ± 4.2 kg/m² (range, 22.1 to 28.3 kg/m²). Overweight is defined as a BMI of 25 kg/m² or greater. On the sleep studies, the respiratory disturbance index (RDI) ranged from 26 to 65 (mean, 45 ± 14.6), and the arterial blood oxygen saturation ranged from 58% to 87% (mean, 66% ± 17.6%). An RDI of more than 10 is diagnostic for OSA syndrome. Twenty-one other patients had collapse of the upper airway at different sites, in addition to a partial or complete obstruction at the level of the laryngeal inlet (deviated nasal septum, bulky redundant soft palate, or hypertrophy of the base of the tongue). These patients were excluded from this study, because they needed additional procedures to alleviate their airway obstructions.

During the same years (1991 through 1997), 38 neonates and infants were referred to us because of severe inspiratory stridor associated with frequent sleep apneas due to laryngomalacia. A fiberoptic laryngoscopic examination was performed in all of these patients while they were awake, and was also performed in 14 infants during sleep (Richards-Wolf flexible nasopharyngolaryngoscope, 2.2 mm) to confirm the diagnosis of laryngomalacia. In 12 cases, the main finding was an abnormally lax and flaccid epiglottis causing obstruction of the airway of sufficient severity to warrant surgical intervention. Sleep studies were performed on these infants, with recording of respiratory effort and arterial blood saturation. All of these patients had from 16 to 43 episodes of obstructive apnea per hour (mean, 27 ± 4.6), of 9 to 23 seconds' duration (mean, 16 ± 2.4 seconds), and all had hypoxemia ranging from 68% to 87% (mean, $79\% \pm 13.4\%$). No patients suffered from central apnea. In this group, there were 7 boys and 5 girls ranging in age from 15 weeks to 32 months. Nine infants presented with significant airway obstruction who had had recurrent hospitalizations and emergency room visits. Six of them required airway support and were intubated for various periods. The other 3 infants had severe feeding difficulties associated with failure to thrive.

Surgical Procedure. Partial epiglottidectomy was the preferred procedure for all our patients, and we used the same surgical technique for both the infants and the adults. All procedures were done under general anesthesia. Airway control was obtained with an aluminum-wrapped red rubber endotracheal tube further protected by a wet cottonoid. Visualization was obtained with the Kleinsasser laryngoscope (adult size for adults and small size for infants) suspended by a Riecker-Kleinsasser chest support. Care was taken not to advance the laryngoscope too far. It was partially withdrawn to expose the valleculae and the base of the tongue with its blade positioned anterior to the epiglottis, thus allowing the epiglottis to fall into the field of view, giving optimal exposure.

A CO₂ surgical laser (Sharplan 791) with a laser-aiming device was fitted to a Zeiss operating microscope equipped with a 400-mm objective lens and a 12.5× eyepiece. The laser was used in a continuous or superpulsated mode with a power setting of 6 to 10 W.

The excision was accomplished after traction was placed on the mid-portion of the epiglottis with a cup forceps. With the epiglottis in maximum traction, a U-shaped wedge was excised from the suprahyoid portion of the epiglottis. The extent of the resection was individualized for each patient according to the

anatomic abnormality causing the obstruction. The lateral sides of the epiglottis (the aryepiglottic folds) were left intact to avoid bleeding from branches of the superior laryngeal vasculature, and to provide the lateral support necessary for normal epiglottic function after the operation.

The CO₂ laser provided a dry operative field during most of the procedure, but when bleeding occurred, hemostasis was maintained with electrocautery of larger vessels.

All patients, infants and adults, were extubated shortly after the completion of surgery. Cardiopulmonary monitoring was applied to all of the patients for 24 to 48 hours after the operation.

A double bolus of dexamethasone sodium phosphate (Decadron), 0.5 mg/kg for infants and 20 to 25 mg for adults, was administered intravenously before induction of anesthesia and 24 hours after surgery to inhibit traumatic edema of the operative field. Perioperative antibiotics were also given to all patients.

Statistical Analysis. Data were analyzed with the paired Student's *t*-test; *p* values less than .05 were considered significant.

RESULTS

Overall, 39 partial epiglottectomies were performed during the years 1991 through 1997: 27 in adults with OSA and 12 in infants with severe laryngomalacia accompanied by frequent apneas, especially during sleep. In all of these cases, the stridor and the apneas were caused by an unusually long, lax, and flaccid epiglottis that collapsed into the laryngeal inlet on inspiration, causing intermittent airway obstruction.

When the infants awakened from anesthesia and extubation, there was a rapid improvement in the stridor, and no more apneas were seen. Within hours, the stridor subsided completely in 10 of the 12 infants, and in the remaining 2, the stridor subsided on the next postoperative day.

In the adult patients, the postoperative oxygen saturation levels were increased from an average of 66% before surgery to an average of 93%, as measured in the recovery room 4 to 6 hours after operation (*p* < .01). No patients required postoperative reintubation or tracheotomy. All of the patients made an uneventful recovery, and there were no serious complications associated with the surgical procedure. There was no postoperative bleeding, dyspnea related to edema, infection, voice change or speech impairment, swallowing difficulty, aspiration, or dysphagia. Pain was usually mild and responded to simple analge-

sics. A liquid diet was initiated on the first postoperative day, after which alimentation was ad libitum.

The patients were discharged from the hospital when adequate oral intake was tolerated. The hospital stay ranged from 3 to 7 days, with an average of 4.3 days. There was no statistically significant difference in the hospitalization period between the infants and the adults.

The patients were followed for 14 to 52 months after operation (average, 32.3 months). All infants had a complete resolution of their symptoms of airway obstruction, with no residual stridor or respiratory distress during sleep or while awake. None of them have had life-threatening episodes of apnea or required further hospitalization related to laryngomalacia or airway obstruction. Among the adult patients, an objective relief of the OSA symptoms was obtained in 23 of the 27 surgical cases (85.2%), mainly in snoring intensity and in daytime sleepiness. Polysomnographic studies were performed in all of the adult patients at least 1 year after operation. The overall decrease in the RDI was from a preoperative value of 45 ± 14.6 to a postoperative value of 14 ± 5.1 ($p < .001$). A statistically significant decrease was achieved in 21 patients (77.8%). In the other 6 patients, the apparent decrease in the RDI was not statistically significant. The overall increase in the blood oxygen saturation levels was from a preoperative value of $66\% \pm 17.6\%$ to a postoperative value of $95\% \pm 13.2\%$ ($p < .001$). A statistically significant increase was found in 23 patients (85.2%). In the other 4 patients, although an impressive increase in oxygen saturation levels was recorded, it was not statistically significant.

Postoperative sleep studies were performed on 7 children during the first year after surgery. Sleep studies were recommended for all infants, but some parents whose children were doing well were reluctant to comply. In all cases, the apneic episodes had disappeared completely and the oxygen saturation levels reached 95% to 97% ($p < .001$). These results coincided with complete cessation of the stridor in these infants.

All patients underwent fiberoptic examination of the larynx between 3 and 12 months after the procedure. No postoperative stenosis was found.

DISCUSSION

Laryngomalacia of infancy and OSA in adults can be causes of serious and life-threatening complications due to associated respiratory difficulties. Worrisome cases may occur when these entities are associated with airway obstruction during sleep, and

severe cases may need urgent surgical intervention.⁹ For surgical management, the anatomic site(s) of obstruction must be identified.⁴

Although laryngomalacia is well recognized in infants, only rare cases have been reported in adults.¹⁷ Laryngomalacia associated with OSA syndrome has been reported by several authors,^{8,21,25} and some studies have implied that there might be an association between a lax and flaccid epiglottis and obstructive apnea in both adults with OSA syndrome and infants with laryngomalacia.^{6,8,9,13-16,19,20,23,31-36}

This study confirms this association and presents our experience with the diagnosis and treatment of patients with OSA and laryngomalacia in whom the obstruction of the airway was the result of an abnormal epiglottis or an abnormal posterior inspiratory displacement of the epiglottis. In our hospital, all patients with a diagnosis of laryngomalacia or OSA undergo transnasal flexible fiberoptic pharyngolaryngoscopy, which has the advantage of observing the larynx in its natural anatomic position and permits observation of the dynamic movements of the epiglottis during inspiration. This procedure is performed in the awake patient and, since 1995, has also been performed during sleep. In all of the cases reported in this study, an abnormal redundant, floppy epiglottis was perceived to cause the respiratory symptoms. At rest, the epiglottis was tilted horizontally and posteriorly against the pharyngeal wall. During inspiration, negative pressure developed within the laryngeal inlet, causing the epiglottis to prolapse downward and inward, resulting in complete airway obstruction. Similar findings have also been reported by other authors.^{6,8,10,15-17,25-27,32,33} In the past, tracheotomy was the standard means of managing patients with abnormalities of the epiglottis that caused severe upper airway obstruction. Some authors proposed a direct surgical approach to the obstruction caused by the epiglottis,⁸ and in the past decade, successful endoscopic resection of redundant and lax epiglottis by means of microlaryngeal surgical techniques and the CO₂ laser was reported.^{22-24,30,36} The laser is easy to manipulate, it shortens surgical time, and it provides a high degree of precision while maintaining hemostasis and minimizing postoperative edema.^{8,21,32} On the basis of our previous experience with other laryngeal disorders, we used the CO₂ laser to treat also obstructions caused by the epiglottis. We performed the same procedure described by Catalfumo et al.³¹ By resection of a U shape of the suprahyoid epiglottis, the flow-induced epiglottis prolapse and the airway obstruction were alleviated. This procedure was found to be both relatively safe and effective and was tolerated well by all our patients, with no complications.

Overall, all of our pediatric patients had complete resolution of their airway obstruction symptoms. Concerning the adults with OSA, by succeeding in locating the exact site of obstruction, we were able to treat and resolve the apneic episodes in as many as 85% of the cases over a long follow-up period. These findings are consistent with results reported by other surgeons.^{6,10,19,25}

We believe that the association of redundancy and flaccidity of the epiglottis and OSA represents a distinct syndrome — epiglottis prolapse-induced obstructive sleep apnea syndrome — and that patients with this abnormality may represent a subgroup of the typical OSA syndrome population.

CONCLUSIONS

This study shows that epiglottis prolapse-induced obstructive sleep apnea syndrome occasionally has a morphological similarity to laryngomalacia of infancy: a redundant floppy epiglottis that prolapses into the laryngeal inlet on inspiration, resulting in

upper airway obstruction. With increasing use of the flexible fiberoptic laryngoscope, which enables direct examination of the dynamic movements of the epiglottis during inspiration, and with a better awareness of this entity, we believe that many cases will be recognized in the future. We found transoral partial epiglottidectomy with the CO₂ laser to be a relatively safe, effective, and relatively simple procedure with no inherent morbidity both in infants with laryngomalacia and in adults with OSA. It provides a high degree of precision while maintaining hemostasis and minimizing postoperative edema, is tolerated well, and has no complications.

Complete relief of the respiratory symptoms was achieved in all the infants who underwent operation and in 85% of the adults in an average follow-up period of 32 months.

Both the immediate and long-term positive results of this procedure confirm its reliability in the management of an appropriately select group of patients with severe laryngomalacia or OSA syndrome.

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LARYNGEAL SARCOIDOSIS: TREATMENT WITH THE ANTILEPROSY DRUG CLOFAZIMINE

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Sarcoidosis is a chronic systemic granulomatous disease that occasionally affects the larynx. When the larynx is affected, the symptoms are frequently mild, but severe airway obstruction can occur. Although systemic corticosteroids are helpful, patients may become refractory to further drug administration. The current methods of treatment are here summarized, and the patient literature is reviewed. We also report a case of a young patient suffering from laryngeal sarcoidosis successfully treated by the antileprosy agent clofazimine and propose it as an alternative treatment of laryngeal sarcoidosis in patients refractory to corticosteroids.

KEY WORDS — airway obstruction, clofazimine, laryngeal sarcoidosis.

INTRODUCTION

Sarcoidosis is a variably disseminated disease involving many body organs. It may be self-limited or progressive, with frequent exacerbations and remissions. It affects the larynx in 0.5% to 8.3% of patients.^{1,2}

The peak age incidence is in the second and third decades; women are more often affected than men.¹ The larynx may be involved in patients with systemic sarcoidosis; it may be the first or only manifestation of disease.³⁻⁵ When the larynx is involved in sarcoidosis, the process tends to affect areas of the larynx that are rich in lymphatics, such as the supraglottis. The endolaryngeal structures affected by laryngeal sarcoidosis, in decreasing order of frequency, are the epiglottis, aryepiglottic folds, false vocal cords, true vocal cords, and subglottis.³

The symptoms are hoarseness, cough, dysphagia, and dyspnea secondary to upper airway obstruction.^{4,6} There is pale pink, edematous, diffuse hypertrophy, especially of the supraglottic area, with the epiglottis being the most affected area,^{5,6} but any portion of the larynx may be affected.

Systemic corticosteroid therapy is the treatment of choice,⁶ but there are reports that unlike the pulmonary and hilar manifestations of the disease, laryngeal lesions do not respond well to systemic ste-

roids.^{7,8} Reviewing the literature, we have identified only 53 cases of isolated laryngeal sarcoidosis.^{3,9} We therefore thought it of interest to report a case of a young patient suffering from sarcoidosis of the larynx who did not respond well to systemic steroids and was cured by the antileprosy agent clofazimine.

CASE REPORT

A 20-year-old man was referred to the otolaryngology department of a university hospital in Freiburg, Germany, for a sleep apnea syndrome of 2 years' duration. In the history, it was elicited that he had undergone a tonsillectomy for chronic tonsillitis 1 year before the appearance of the symptoms of sleep apnea.

In the last 2 months, the sleep apnea had worsened, and the patient had had to be hospitalized for respiratory difficulties. On admission, the patient was in progressive respiratory distress with distinct inspiratory stridor. On indirect laryngoscopy, the epiglottis, aryepiglottic folds, and false vocal cords were markedly swollen. The true vocal cords appeared to be normal, with normal movement. The airway was at about 70% of the normal capacity. No other findings were noted in the otolaryngological examination.

The findings on physical examination were normal, as were those of chest radiography and routine laboratory tests. Sputum staining for acid-fast bacte-

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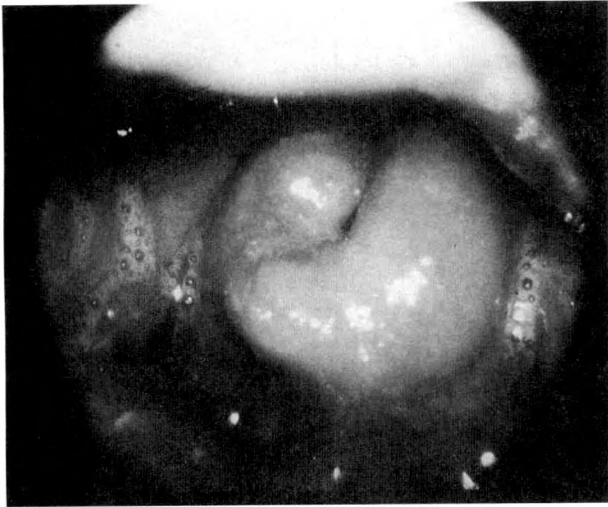


Fig 1. Diffuse, symmetric enlargement of epiglottis with significant airway obstruction.

ria and intradermal tests for tuberculosis were negative. Serologic studies for syphilis, cat-scratch disease, and histoplasmosis were also negative. Magnetic resonance imaging of the larynx showed a diffuse swelling of the internal larynx and the epiglottis. Under general anesthesia, direct laryngoscopy was performed and confirmed the findings of indirect laryngoscopy (Fig 1). Biopsy specimens were taken from the epiglottis and aryepiglottic folds. The biopsies revealed a noncaseating granulomatous laryngitis that was diagnosed as sarcoidosis (Fig 2). Acid-fast bacilli could not be seen on direct microscopy and were not recovered in the culture of the biopsy material. Special fungal cultures and stains for blastomycosis, coccidioidomycosis, and candidiasis were all negative.

In accordance with the histologic findings, the patient was placed on a therapeutic dose of prednisone



Fig 3. Regression of epiglottic swelling after 10 days of treatment with clofazimine. Epiglottis shows residual status of omega form.

(1 mg/kg) for 3 months. As his symptoms did not subside, the prednisone dose was increased to 2.5 mg/kg, and after 6 months of treatment, the symptoms and laryngeal appearance did not change. The patient firmly refused any surgical intervention.

The cortisone treatment was stopped, and a tentative treatment with clofazimine 100 mg daily was initiated. After 10 days of treatment, the airway was much improved, and some regression of the swelling could be noted (Fig 3). Thereafter, 200 mg of clofazimine 3 times a week was given for 10 weeks. Under this treatment, the respiratory difficulties receded rapidly, and examination of the larynx showed a significant resolution of the enlargements. No side effects were observed. The patient was followed up for a period of 4 years without recurrence.

DISCUSSION

Although laryngeal sarcoidosis was recognized in



Fig 2. View of epiglottic mucosa showing multiple subepithelial granulomas surrounded by dense inflammatory infiltrate (original $\times 40$).

the first decade of the 20th century, the first pathologically confirmed case was described only in 1940.¹⁰

Most patients commonly present with hoarseness, dyspnea, and dysphagia, as in our case.^{5,6,11,12} The epiglottis is most commonly involved, followed by the remaining supraglottic structures, but every part of the larynx can be involved in the disease.^{5,6-8} The diagnosis is made by laryngeal biopsy, and the histologic appearance of sarcoidosis in the larynx is the same as that in other sites.¹¹

Caseating granulomas, composed of large polyhedral epithelioid cells with pale eosinophilic cytoplasm, are characteristically present; giant cells of the Langerhans type surrounded by inflammatory cells are present, but they are not required for pathological diagnosis.^{6,7,11}

When necrosis occurs, it is fibrinoid, and older lesions become fibrotic and hyalinized, indicating inactivity of the disease.¹¹ Specific infectious granulomatous diseases such as tuberculosis, syphilis, cat-scratch disease, and laryngoscleroma can be excluded by appropriate staining or serologically.² Necrotizing vasculitis and glomerulitis are features of Wegener's granulomatosis that do not occur in sarcoidosis.

The treatment of choice is long-term administration of cortisone at a low dosage.^{5,6,8,11,13} Laryngeal sarcoidosis may be life-threatening, as patients can develop airway obstruction and may require a tracheotomy. In Devine's¹⁴ study, 8 patients developed airway obstruction, and 5 required a tracheotomy. Ruff and Bellens¹⁵ reported a case of sarcoidosis of the larynx with airway obstruction successfully treated by a CO₂ laser.

Because the disease has a tendency toward spontaneous regression, patients who have mild or moderate airway symptoms can be followed up on a regular basis, and when severe airway obstruction occurs, a high dose of systemic steroids may relieve the edema.¹¹ Intralesional injections of steroids are sometimes effective, but this technique is only applied to patients with well-circumscribed disease and requires direct laryngoscopy.^{7,8,11,16}

Carasso¹² reported a patient with systemic manifestations of sarcoidosis who developed laryngeal involvement with airway obstruction and was successfully treated by irradiation at a total dose of 30 Gy to the larynx.

Fogel et al¹⁸ reported a case of laryngeal sarcoidosis refractory to corticosteroids that was treated with megavoltage radiotherapy as an alternative to tracheotomy.

In 1984, Neuhofer and Fritsch¹⁷ reported a pilot

study with the antileprosy agent clofazimine on 7 patients with cheilitis granulomatosa or complete Melkersson-Rosenthal syndrome. Beneficial effects were observed in all patients, and after drug withdrawal, 4 patients remained free of symptoms for periods ranging from 5 to 45 months.

In 1986, Podmore and Burrows¹⁸ treated 3 cases of Miescher's granulomatous cheilitis and 1 case of Melkersson-Rosenthal syndrome for a 4-month period with clofazimine. They reported that all cases showed histologic improvement, with clearance of granulomas.

Clofazimine is a phenazine iminoquinone derivative that is metabolized to a red dyestuff with oxygen. It is taken up by the reticuloendothelial system and fatty tissue on prolonged administration and may produce a reddish brown pigmentation that increases with ultraviolet exposure.¹⁸

The mechanism of action of clofazimine is not fully known, but is thought to be related to its ability to stimulate phagocytosis.¹⁷⁻²¹ Clofazimine is a relatively safe drug if used in short courses and in low dosages, with the only side effect being a red discoloration of the skin. However, there have been some reports of eosinophilic enteritis after 600 mg of clofazimine daily for a 3-year period in leprosy patients in India.^{19,22}

Neuhofer and Fritsch¹⁷ and Podmore and Burrows,¹⁸ who treated Melkersson-Rosenthal cheilitis with low dosages of clofazimine, did not report any side effects, and concluded that it appears to be a relatively safe, therapeutically effective drug.

Our patient was a 20-year-old man suffering from sarcoidosis of the larynx with dyspnea that was refractory to systemic corticosteroids. There were no other manifestations of sarcoidosis. Because his laryngeal lesion was not well circumscribed, he was not suited to intralesional injection of corticosteroids, and airway obstruction was impending. We considered radiotherapy, but the experience with radiotherapy is limited, and failures outnumber successes.¹¹ On the basis of the literature and on a former case of Melkersson-Rosenthal syndrome successfully treated in our clinic by clofazimine, we decided to treat our young patient with this drug. The results after a low dosage of clofazimine (100 mg for 10 days) showed a rapid improvement without any side effects. Clofazimine has also proved effective in the treatment of pyoderma gangrenosum, discoid lupus erythematosus, and pustular psoriasis, in which the mechanism of action may also be due to enhanced macrophage phagocytosis.¹⁸

Although our experience is based on 1 case, we

suggest clofazimine as an alternative in the treatment of laryngeal sarcoidosis refractory to systemic corti-

costeroids, and it seems to us that clofazimine in low dosage is an effective and relatively safe drug.

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RESPONSE OF THE CRICOTHYROID AND THYROARYTENOID MUSCLES TO STEREOTACTIC INJECTION OF SUBSTANCE P INTO THE REGION OF THE NUCLEUS TRACTUS SOLITARIUS IN DEVELOPING DOGS

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Substance P (SP), a putative sensory neurotransmitter, mediates reflex laryngeal adductor activity in developing dogs. Such reflex activity includes life-threatening laryngospasm induced by stimulation of distal esophageal afferent nerves. The site of SP's activity is unknown. This research was undertaken to determine whether injection of SP into the nucleus tractus solitarius (NTS) of developing beagles alters laryngeal adductor motor activity. Six animals, 57 to 78 days of age, underwent stereotactic injection of 5 to 10 μ L of SP into the region of the NTS, identified by electrical stimulation of the ipsilateral superior laryngeal nerve. In 8 additional studies, SP was injected into the cerebellum (2) or brain stem (6) distant from the NTS. Cardiovascular and electromyographic (EMG) responses of the diaphragm and the cricothyroid (CT) and/or thyroarytenoid (TA) muscles were recorded in all 6 animals. Injection of SP into the region of the NTS induced a decrease in blood pressure in all animals and an increase in either ipsilateral CT or TA activity. Three of these animals experienced mixed apnea characterized by sustained EMG activity (spasm) of the ipsilateral CT or TA muscles and an absence of diaphragm EMG activity. The apnea event was fatal in 1 of these animals. In the 6 animals who underwent injections in the brain stem but outside the region of the NTS, diaphragm and laryngeal EMG activity generally did not change after injection of SP, with the exception of 1 animal who experienced a mild, short-lived increase in ipsilateral CT activity. A brief phasic increase in ipsilateral CT activity was seen in both animals who underwent injection of SP into the cerebellum. A putative sensory neurotransmitter, SP evokes ipsilateral CT and/or TA EMG activity when injected into the region of the NTS in developing beagle dogs. This research suggests that SP in the NTS may play a role in mediating life-threatening laryngeal adductor reflexes in developing mammals and may provide important information regarding therapeutic intervention.

KEY WORDS — cricothyroid muscle, dog, electromyography, laryngospasm, nucleus tractus solitarius, substance P, thyroarytenoid muscle.

INTRODUCTION

Developing mammals are subject to life-threatening laryngeal adductor reflex responses, including the well-described laryngeal chemoreflex¹⁻³ and the esophagolaryngeal adductor reflex.⁴ These reflex responses are postulated to occur in infants and are implicated in certain cases of sudden infant death syndrome, particularly because some postmortem studies suggest that the infants succumb to laryngospasm. Little is known about the neurotransmitters and the neural pathways that mediate reflex laryngeal adductor activity in developing animals. Such information may prove useful in managing these potentially life-threatening laryngeal reflexes.

Substance P (SP) is a member of the family of tachykinins, a group of biologically active peptides. It is often found to be co-localized with other peptides and neurotransmitters and is thought to act pri-

marily as a sensory neurotransmitter.⁵ Intravenous injection of SP in dogs increases electromyographic (EMG) activity of the thyroarytenoid muscle (TA) and cricothyroid muscle (CT), particularly in young, developing dogs.⁶ The potentially life-threatening esophagolaryngeal adductor reflex, induced by nociceptive stimulation of the distal esophageal afferents in developing dogs, appears to be mediated by SP, because pretreatment with a pharmacological SP antagonist abolishes the response (unpublished observations).

The site at which intravenous SP exerts its effect on laryngeal motor activity is unknown. Transection of the vagus nerve blocks the increase in adductor motor activity, indicating that the response does not occur at the neuromuscular end plate.⁶ Immunoreactivity to SP is present in afferent vagal nerve fibers, in the nodose and jugular ganglia,^{7,8} and in the

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nucleus ambiguus and the nucleus tractus solitarius (NTS). This finding suggests that SP may exert its effect on laryngeal motor activity at any of these sites.

In this study, we sought to determine whether injection of SP into the NTS alters laryngeal motor adductor activity. Because SP is thought to act primarily as a sensory neurotransmitter, the NTS was chosen as the site of study in this investigation. The NTS is the primary site of termination of the laryngeal afferent fibers,^{9,10} and transection of the vagus nerve reduces SP-like immunoreactivity in the NTS.¹¹

METHODS

Conditioned beagle puppies were anesthetized with intravenous pentobarbital sodium (25 mg/kg), which does not appear to blunt the laryngeal reflexes. A femoral arterial catheter was placed percutaneously or via a small cutdown incision and attached to a pressure transducer. The trachea and larynx were exposed by a ventral midline incision, and a tracheotomy tube was placed through the interspace between the third and fourth tracheal rings. The animal breathed spontaneously throughout the procedure. The animal was placed on a warming blanket, and its body temperature was maintained at approximately 37°C.

Bipolar hooked wire electrodes were inserted into the CT and TA to monitor the EMG activity of the primary laryngeal adductor muscles, and into the diaphragm to monitor respiratory activity. Cuff electrodes were placed around the internal branch of the superior laryngeal nerves bilaterally. All electrode wires were secured to adjacent soft tissue to prevent dislodgment during the procedure. Responses of the EMG electrodes and pressure transducer were viewed on-line via a computer monitor with data acquisition software (Windaq). Signals were low-pass-filtered at 500 Hz and then digitized at a sampling rate of 1 kHz per channel and transferred to a magnetic optical disk for subsequent analysis.

The animal was rotated into the prone position, and the head was secured in a stereotactic frame (model 1430 with dog adapter, Kopf Instruments, Tujunga, Calif). An occipital scalp incision was made, and the occipital muscles were divided at the midline with electrocautery and retracted laterally to expose the occiput. The occipital bone overlying the cerebellum was thinned with a diamond bur, and rongeurs were used to create a 1.0- to 1.5-cm hole in the bone. The dura was divided and the cerebellum exposed.

A brain atlas for beagle pups is not available, so the coordinates of the NTS were estimated from those found in an adult beagle atlas.¹² Coordinate values were based on the distance from "ear bar zero." Ear bar zero was defined as the midpoint between the

two ear bars in the anterior-posterior (A-P), medial-lateral (M-L), and dorsal-ventral (D-V) axes and was determined before placing the animal in the stereotactic frame. Coordinate values were expressed in millimeters from ear bar zero, with positive values reflecting anterior, medial, and dorsal positions.

A monopolar microelectrode was used to record action potentials from the brain stem. The microelectrode had been fashioned from an epoxy-insulated 0.2-mm-diameter tungsten wire electrolytically etched to a very fine point. The electrode shaft was stiffened by ensheathing it in a stainless steel tube that extended to within 1 cm of the tip. The sheath and the tip of the electrode were insulated except for 0.1 mm of the electrode's tip. The microelectrode was inserted into the cerebellum at an angle 15° posterior to the coronal plane on the theory that this angle minimizes damage to the brain and to the electrode from the bony tentorium.¹³ The predetermined stereotactic coordinates were adjusted trigonometrically to reflect this insertional angle. The microelectrode was positioned on the basis of the A-P and M-L coordinates and was slowly lowered ventrally. When the tip of the electrode was within 4 mm of the D-V coordinate, the internal branch of the superior laryngeal nerve was stimulated to identify the NTS. Rectangular, monophasic, constant-current electrical pulses were delivered to the superior laryngeal nerve via a Grass nerve stimulator (Grass Medical Instruments, Quincy, Mass) at a rate of 1 pulse per second with 2-ms duration, at a current level between 2 and 15 mA. Responses detected by the monopolar microelectrode were viewed on an oscilloscope. The electrode was lowered in the dorsal direction until a reproducible, consistent action potential was seen, which began about 4 ms after the stimulus was delivered. Cell activity was not seen unless a stimulus was delivered. If a response was not seen by the time the electrode reached ear bar zero in the D-V plane, the electrode was removed and reinserted 0.5 mm anterior, posterior, medial, or lateral to the previous insertion coordinate. This technique was systematically repeated until a reproducible response was seen.

When the presumed site of the NTS was located, the stereotactic coordinates were recorded and the microelectrode was removed. A 30-gauge, 2-inch stainless steel needle (Hamilton Company No. 0160830, Reno, Nev), insulated except for the last 0.1 mm of the tip, was inserted according to the A-P, D-V, and M-L coordinates identified by the microelectrode. If many insertional tracks had been required to locate the NTS, the needle was usually inserted at the same A-P and D-V coordinates, but on the opposite side of the brain stem. Once positioned, 5 μ L of SP (1 μ g/ μ L) was slowly injected. Responses of the dia-

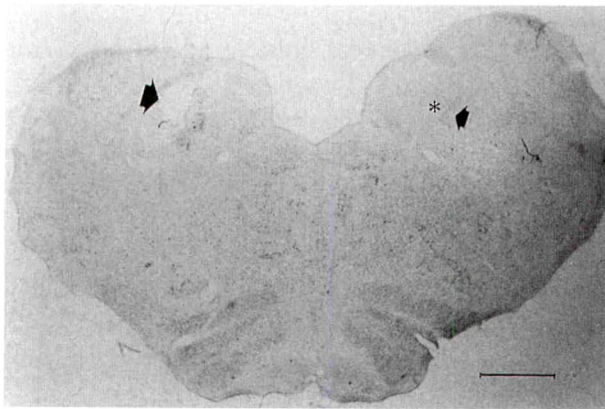


Fig 1. Axial brain stem section, stained with cresyl violet, from beagle (study 3) who experienced marked increase in ipsilateral thyroarytenoid electromyographic (EMG) activity after substance P (SP) injection into nucleus tractus solitarius (NTS). Note electrolytic lesion marking site of injection into NTS (large arrow). Contralateral nucleus (small arrow) and tract (asterisk) of NTS are indicated. Bar — 1.5 mm.

phragm, ipsilateral CT and TA and contralateral CT EMG responses, heart rate, and blood pressure were recorded. In control studies, SP was injected into the cerebellum or the brain stem remote from the NTS.

After the animal's vital signs and EMG responses had returned to baseline, an electrical lesion at the injection site was created by delivering a 1-mA direct current to the needle electrode for 20 seconds. At the conclusion of the investigation, the animals were euthanized with 80 mg/kg of intravenous pentobarbital sodium. The brain stems were harvested to determine the injection site of the SP after perfusion of the animals with 10% buffered formalin via the left ventricle. Fifty-micron-thick tissue sections were cut every 1 mm with a freezing cryostat. The

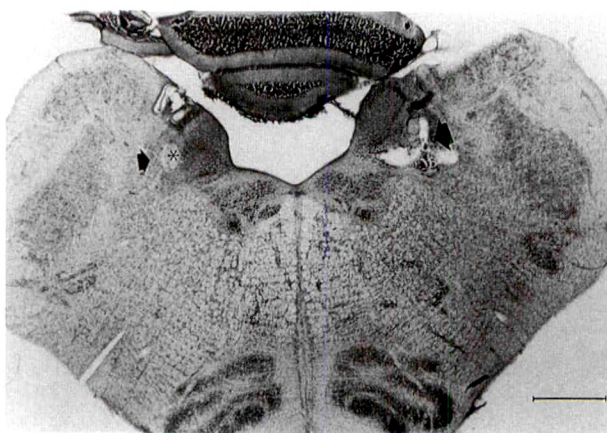


Fig 2. Axial brain stem section, stained with cresyl violet, from beagle (study 5) in whom SP infusion induced increase in ipsilateral and contralateral cricothyroid EMG activity, as well as central apnea. Note electrolytic lesion marking site of injection into NTS (large arrow). Contralateral nucleus (small arrow) and tract (asterisk) of NTS are indicated. Bar — 1.5 mm.

TABLE 1. COORDINATE VALUES RELATIVE TO EAR BAR ZERO FOR SP INJECTIONS INTO REGION OF BEAGLE NTS

Subject	Age (d)	Weight (kg)	A-P (mm)	M-L (mm)	D-V (mm)
1	71	4.2	7.0	2.0	5.0
2	78	3.8	4.8	2.3	5.0
3	69	2.8	6.7	3.0	3.5
4	74	3.0	3.9	4.5*	3.0
5	57	1.6	6.7	2.0	5.0
6	67	2.8	8.9	2.4	4.6
Mean	69	3.0	6.3	2.7	4.4

Data confirmed histologically. SP — substance P, NTS — nucleus tractus solitarius, A-P — anterior-posterior, M-L — medial-lateral, D-V — dorsal-ventral.

*Tip of injection site touched lateral edge of NTS.

sections were prepared, stained with cresyl violet, and mounted on a glass slide for review with a light microscope.

The response parameters were compared with the baseline values measured immediately before SP injection. Changes in heart rate, respiratory rate, and blood pressure were compared with Student's paired *t*-tests, with *p* values of <.05 reported as significant. Changes in laryngeal EMG activity were assessed qualitatively.

RESULTS

Fourteen studies were completed in 6 animals. The animals ranged in age from 57 to 78 days (mean, 70.3 days) and ranged in weight from 1.4 to 4.2 kg (mean, 3.0 kg). All animals were spontaneously ventilating during the time of the study, except for 1 animal (No. 3), which required mechanical ventilation. Injection of SP into the NTS was attempted in 9 studies. Histologic review confirmed that SP was injected into the NTS in 6 of these 9 studies (Figs 1 and 2). The brain stem coordinates that provided access to the NTS in the developing beagle pups are listed in Table 1 along with the weights and ages of the animals. The mean coordinate values were 6.3 mm posterior to ear bar zero (A-P), 2.7 mm (M-L), and 4.4 mm superior to ear bar zero (D-V). Most variability occurred in the A-P coordinates. This variability did not correlate with the weight of the animal ($R = -.19$). Substance P was intentionally injected into areas remote from the NTS in 5 control animals (Fig 3). In 3 additional control animals, the SP injections were intended to be in the NTS, but on postmortem histologic assessment were noted to be in remote areas.

Laryngeal and Respiratory Response. The CT, TA, and diaphragm EMG activity was recorded (Tables 2 and 3). Only 4 EMG recordings could be obtained in each study, so data for the contralateral TA and/or diaphragm are not available in some studies. The CT

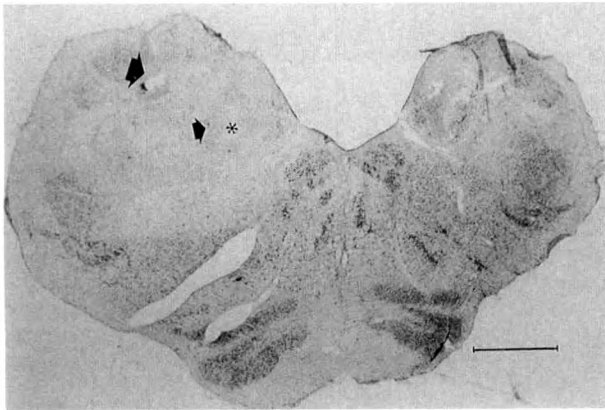


Fig 3. Axial brain stem section, stained with cresyl violet, from beagle (study 8). Note electrolytic lesion (large arrow) indicating site of SP injection in gracile fasciculus, lateral to NTS tract (asterisk) and nucleus (small arrow). Laryngeal adductor and diaphragm EMG activity remained unchanged after infusion; blood pressure decreased. Bar — 1.5 mm.

and/or TA EMG activity ipsilateral to the NTS injection increased in all 6 subjects (Table 2). Ipsilateral CT EMG activity increased in 4 of the 6 animals, usually in a phasic pattern, and contralateral CT EMG activity increased in 3 of these 4 animals (Figs 4 and 5). Ipsilateral TA EMG activity increased in 3 animals in a continuous pattern of firing suggesting spasm of the muscle (Fig 5). Contralateral TA activity did not increase in the 1 animal in which it was recorded. Central apnea was observed in 2 subject animals and verified by the absence of diaphragm EMG activity. In 1 of these animals, the apnea was fatal. Although this animal had both central and obstructive apnea, the central apnea was likely the cause of its demise, because the tracheotomy bypassed any obstruction at the laryngeal level. In the remaining animals, the mean respiratory rate was not significantly altered by the infusion of SP ($p > .10$). The

CT and TA EMG activity remained unchanged in 5 of the 6 animals that underwent injections into the brain stem in sites other than the NTS (Fig 6). One animal (No. 14), in whom SP was injected close to the NTS, experienced a mild phasic increase in ipsilateral CT activity that was brief in duration. The relative proximity of the injection site to the NTS may account for the mild activity seen. A mild, phasic increase in ipsilateral CT activity was also observed in 2 animals in which SP was injected into the cerebellum. Infusion of SP did not alter the mean respiratory rate in any of these control animals ($p > .05$). Other reactions to SP, such as vomiting, sneezing, and coughing, did not occur in any animal.

Cardiovascular Response. Blood pressure decreased in all animals who underwent SP injections to the region of the NTS (Tables 2 and 3). The change was evident a mean of 22.9 seconds after infusion of SP. Blood pressure decreased in 2 of the 7 control animals that underwent brain stem injections to the cuneate nucleus and the gracile fasciculus. However, the mean percent change in blood pressure in subject animals was greater than that in control animals ($p < .05$), as was the decrease in heart rate ($p < .05$).

DISCUSSION

The findings of this study suggest that injection of SP into the region of the NTS elicits an increase in laryngeal motor activity that is generally absent when it is injected into the brain stem region outside the NTS.

It is not known whether our findings in an animal model correlate with responses that occur in humans. Understanding the mechanism of SP in causing potentially life-threatening laryngeal adductor reflex responses in developing animals, however, may be an

TABLE 2. SUBJECT RESPONSES TO INJECTION OF SP INTO REGION OF NTS

Study	Ipsilateral CT	Contralateral CT	Ipsilateral TA	Contralateral TA	Blood Pressure	Diaphragm
1	+ Phasic at 49 s × >450 s	+ Phasic at 49 s × >450 s	—	NA	Decrease at 18 s	NA
2	+ Spasm at 10 s × 82 s	+ Spasm at 10 s × 12 s	+ Spasm at 10 s × 2 s	NA	Decrease at 14 s	Apnea at 10 s × 82 s
3*	—	—	+ Spasm at 3 s × 26 s	—	Decrease at 43 s	NA
4†	+ Phasic at 7 s × 21 s	—	—	NA	Decrease at 23 s	+ Phasic
5	+ Phasic at 16 s × >100 s	+ Phasic at 16 s × >70 s	—	NA	Decrease at 26 s	Apnea at 7 s × 12.5 s
6	—	—	+ Spasm at 3.5 s × 110 s	NA	Decrease at 13.4 s	Apnea at 22 s × 120 s, then animal died

Data confirmed histologically. NA — not available.

*Animal required mechanical ventilation.

†Injection site at edge of NTS.

TABLE 3. CONTROL (NON-NTS) RESPONSES TO SP INJECTION

Study	Site	Ipsilateral CT	Contralateral CT	Ipsilateral TA	Contralateral TA	Blood Pressure	Diaphragm
7	Brain stem (cuneate nucleus and reticular formation)	—	—	—	NA	Decrease at 12 s	—
8	Brain stem (gracile fasciculus)	—	—	—	NA	Decrease at 22 s	—
9*	Brain stem	—	—	—	NA	—	—
10	Brain stem	—	—	—	NA	—	—
11*	Brain stem	—	—	—	NA	—	—
12	Cerebellum	+ Phasic, minimal	—	—	NA	—	—
13*	Cerebellum	+ Phasic, minimal	—	—	NA	—	—
14	Brain stem	+ Phasic, minimal	—	—	NA	Decrease	—

*Animals in whom SP was intended to be injected into NTS but in whom histologic examination disclosed injection site to be remote from NTS.

important step in preventing such responses in humans. Laryngospasm is postulated to account for some cases of sudden infant death syndrome and is a well-recognized and dreaded complication of general anesthesia in infants and children. In clinical trials, an SP antagonist selective for the neurokinin-1 receptor proved effective in preventing postchemotherapy nausea and vomiting mediated through the NTS.¹⁴ These studies suggest that SP antagonists may prove effective in preventing life-threatening laryngeal adductor reflexes in infants and perhaps in preventing intraoperative laryngospasm.

The NTS is a primary center for the relay of peripheral sensory nerve input and likely plays an important role in regulating laryngeal function. The NTS receives projections from the 5th, 7th, 9th, and 10th cranial nerves, including the superior laryngeal nerve, the primary sensory nerve of the larynx.^{15,16} The NTS plays an important role in effecting behavioral, neuroendocrine, and autonomic responses by

projecting to other regions of the brain stem and brain.

In the absence of a stereotactic atlas for beagle pups, the NTS was identified in these studies by stimulating the ipsilateral superior laryngeal nerve and locating consistent, reproducible action potentials from the region of the NTS — similar to techniques used to elicit vocalization in dogs.¹³ Histologic analysis of the brain stems revealed this to be an accurate means of identifying the region of interest. Most of the variation in coordinate values between subject animals occurred in the A-P direction, and it may reflect our variability in placement of the ear bars in the A-P plane. Identification of the NTS would likely have been facilitated by removal of the cerebellum, but this was not performed because of concern that the laryngeal response might be altered.

The NTS is divided into subnuclei, several of which likely play a role in mediating the laryngeal responses seen in this study. In ferrets, afferent fibers of the superior laryngeal nerve project to the dorsal and dor-

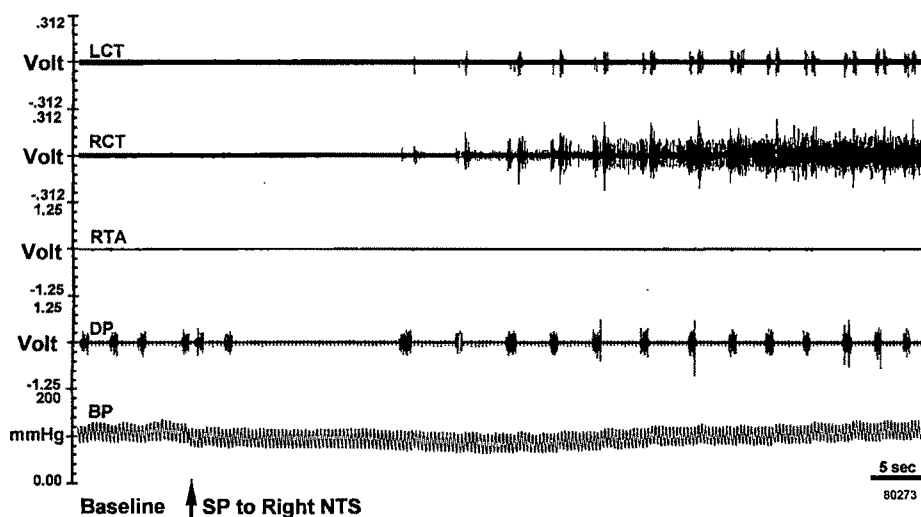
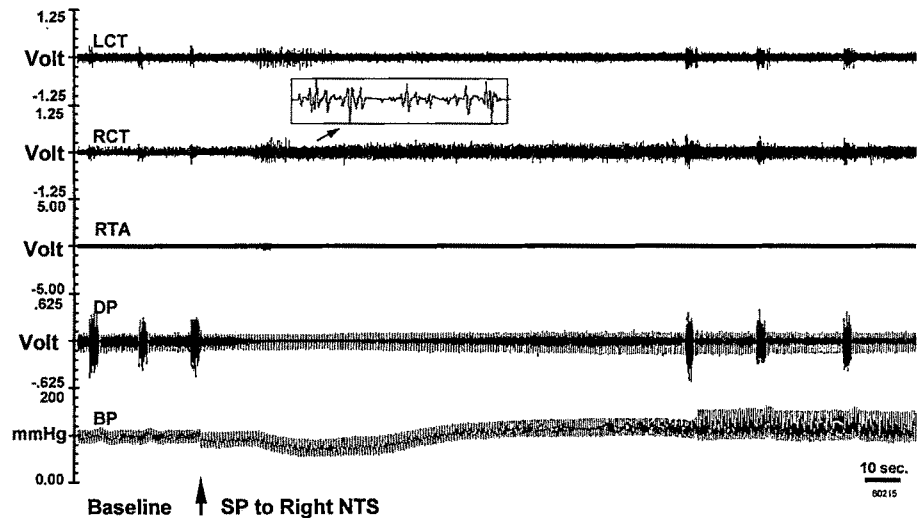


Fig 4. Tracing from 57-day-old dog (study 5) after injection of SP into right NTS. Note marked increase in right cricothyroid EMG (RCT) and left cricothyroid EMG (LCT) signals after SP injection. Note also absence of diaphragm EMG (DP) signal, indicating central apnea, and accompanying decrease in blood pressure (BP). RTA — right thyroarytenoid EMG.

Fig 5. Tracing from 78-day-old dog (study 2) after injection of SP into right NTS. Note nonphasic (spasmodic) increase in RCT and brief spasm in LCT 10 seconds after injection. Inset shows enlargement of characteristic motor action potentials. Note also concomitant activity from RTA of very short duration. Absence of phasic DP signal indicates that animal also experienced central apnea. BP diminished after SP injection.



solateral, medial, and interstitial subnuclei of the NTS.¹⁷ In rats, the central part of the NTS projects to the rostral part of the nucleus ambiguus,¹⁵ the periaqueductal gray area, and the nucleus retroambiguus. It is probable that these projections are involved in mediating the laryngeal motor response induced by application of SP to the laryngeal sensory nucleus.

Two of the 3 animals that demonstrated continuous (nonphasic) TA EMG activity also developed central apnea, which caused the death of 1. No EMG data were available for the diaphragm in the third animal. Laryngospasm and central apnea have both been implicated as possible causes of sudden infant death syndrome,¹⁸⁻²² and the findings of these studies may provide a possible mechanism for such phenomena.

It is unclear why ipsilateral CT or TA EMG activity increased in 5 of the 6 study animals and increased in both muscles in only 1 animal. It is possible that the premotor neurons in the canine NTS are topographically arranged by subnuclei and that our injections

did not encompass both the CT and TA regions. Our electrolytic lesion marking the site of SP injection usually engulfed the entire diameter of the NTS and precluded our ability to distinguish the subnuclei of the NTS.

The dorsal motor nucleus of cranial nerve X (DMN) is located close to the NTS, and it is possible that some of the presumed vagal excitatory effects of SP seen in this study were due to stimulation of postsynaptic neurons in the DMN. The 5 to 10 μ L of SP that was injected in each animal likely diffused at least 1 mm in each direction.²³ Although our electrolytic lesion did not involve the DMN, it is possible that SP diffused beyond the area marked by the lesion and stimulated the DMN. The DMN does not appear to receive projections from the superior laryngeal nerve, but retrograde horseradish peroxidase staining suggests that the nucleus does provide motor innervation to the larynx.⁹

The vasopressor effect of SP injection into the region of the NTS may reflect direct vagal excitatory

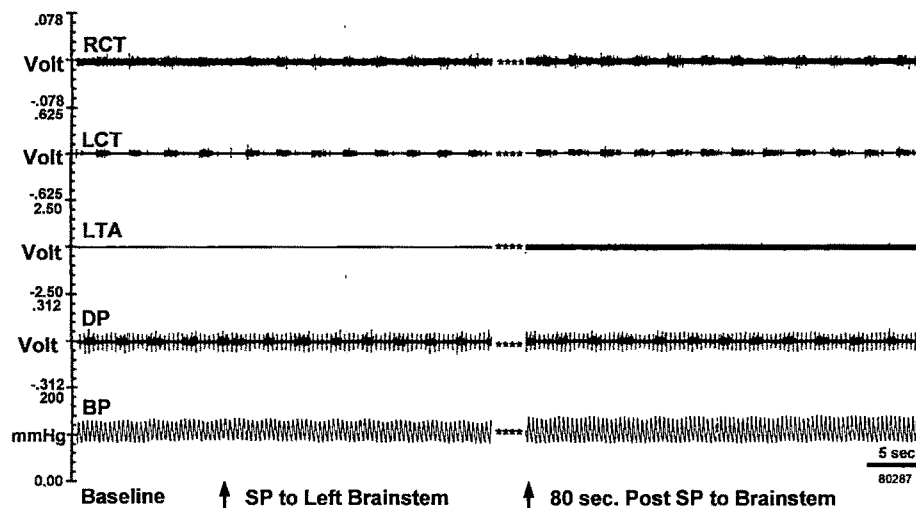


Fig 6. Tracing (study 10) after injection of SP into left brain stem remote from NTS. Note absence of change in EMG activity of RCT, LCT, left thyroarytenoid EMG (LTA), and DP. BP also remains unchanged after infusion.

effects or, alternatively, may reflect interaction with the postsynaptic projections of the carotid sinus nerve. The NTS receives projections from the carotid sinus nerve, and the nucleus is thought to be an integral site in mediating cardiovascular responses.²⁴ Mifflin²⁵ found that nearly half of the cells in the NTS that responded to superior laryngeal nerve stimulation also responded to electrical stimulation of the carotid sinus nerve.

Two control animals who underwent injection of SP in other regions of the brain stem also experienced a decline in blood pressure. One of these animals underwent an injection into the region of the cuneate

nucleus, and 1 into the reticular formation. Projections from the carotid sinus nerve to the cuneate nucleus have been identified in dogs,²⁶ and perhaps account for the blood pressure changes seen in 1 of these animals.

SUMMARY

Injection of SP, a putative sensory neurotransmitter, into the region of the NTS increases ipsilateral CT and/or TA motor activity and has a vagal excitatory effect on blood pressure and heart rate in developing beagles. Substance P may be an important neurotransmitter in the mediation of reflex responses involving laryngeal adduction in developing mammals.

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CARTILAGE GENERATION USING ALGINATE-ENCAPSULATED AUTOGENOUS CHONDROCYTES IN RABBITS

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In this study, we investigated the possible use of calcium alginate as a matrix for cartilage generation with autogenous chondrocytes, and examined whether the generated cartilage could keep its original volume over time when used as an implant for filling and contour restoration in the host body. Biodegradable, biocompatible, and injectable calcium alginate impregnated with isolated autogenous chondrocytes from the auricle was injected into the gluteus muscle of 12 New Zealand White rabbits. The volume of injected calcium alginate was always 3 mL, and the density of chondrocytes was 10×10^6 cells per milliliter. At 4 weeks (short-term period, $n = 6$) and 20 weeks (long-term period, $n = 6$) after injection, the histologic findings and the volume of the generated cartilaginous nodules were analyzed. At the time of harvest, 10 of the 12 specimens revealed findings characteristic of natural cartilage. However, histologic examination demonstrated scanty vascular and fibrous tissue ingrowth. Many osteoid matrices, including marrow-like cells, were noted in the vicinity of the neocartilage. The approximate original volume of the injected material was maintained over 20 weeks. These results suggest that although complete cartilage replacement was not always achieved, calcium alginate-autogenous chondrocytes may represent an injectable implant that can generate new autogenous fibro-osteo-cartilaginous tissue for volume augmentation.

KEY WORDS — calcium alginate, cartilage, implant, tissue engineering.

INTRODUCTION

Autogenous cartilage could be used as a graft for cosmetic improvement or reconstruction, but there are some problems with supply, donor site morbidity, and scarring. Recent developments in the field of tissue engineering provide novel approaches to tissue repair and reconstructive surgery.¹⁻⁴

Vacanti et al⁵⁻⁷ demonstrated a new technology whereby isolated chondrocytes can be combined with a biocompatible polymer scaffold to create an implant that has the ability to generate new cartilage. In their study, large amounts of bovine chondrocytes were harvested, seeded onto polymeric templates, and implanted into athymic mice. Use of an immune-incompetent recipient avoids host rejection of the chondrocyte xenograft. For clinical application of this technology, there is a need to determine whether autogenous tissue-engineered cartilage can be synthesized in an immune-competent host.

In otolaryngological and reconstructive surgical fields, injection of polytetrafluoroethylene (Teflon) or collagen has been used for filling and contour restoration. However, particle migration to distant organs has raised concerns regarding the use of Teflon paste, and the high rate of re-treatment required because of implant volume loss has limited the usefulness

of collagen. The ideal implant material should be nonmigratory and nonantigenic, and the delivery should be minimally invasive.

Calcium alginate is a polysaccharide polymer isolated from seaweed. It has been studied as an external matrix for chondrocytes for cartilage generation by tissue engineering techniques because of its biocompatible, bioresorbable, and injectable characteristics.^{8,9}

In this study we investigated the possibility of using calcium alginate as an injectable matrix for cartilage generation with autogenous chondrocytes. We also examined whether the generated cartilage would keep its original volume over a long period of time as an implant for filling and contour restoration in the immune-competent host body.

MATERIALS AND METHOD

Cartilage Harvesting and Chondrocyte Isolation. Twelve New Zealand White rabbits weighing between 1.8 and 2.0 kg were used. General anesthesia was induced by an intramuscular injection of ketamine hydrochloride at 50 mg/kg. After preparation and infiltration of the local anesthetic agent, the right ear was harvested. The overlying skin and perichondrium were removed, and about a 3 × 3-cm piece of

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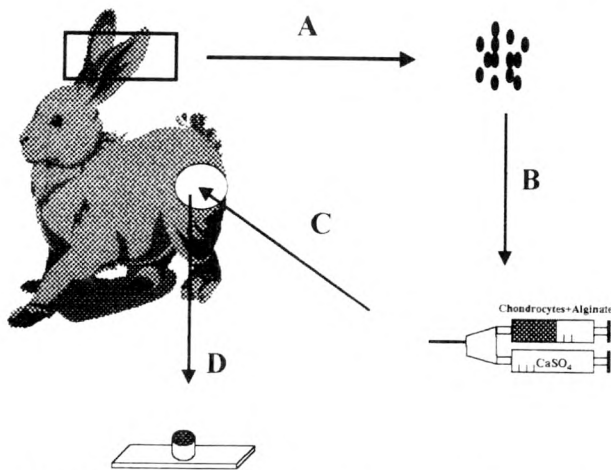


Fig 1. Schematic representation of experiment. A) Chondrocytes were isolated by means of enzyme digestion of auricular cartilage matrix. B) Cell pellet was resuspended in 1.8% sterile liquid sodium alginate to yield cellular density of 10×10^6 cells per milliliter. For simultaneous injection, 200-mmol/L sterilized calcium sulfate was added to suspension for alginate polymerization by Pantaject dual injection set. C) Alginate with viable autogenous chondrocytes was injected into rabbit's gluteus muscle. D) Four or 20 weeks after injection, implanted material was evaluated grossly and histochemically.

auricular cartilage was obtained. The cartilage was minced to 1 mm^3 , and the extracellular matrix was digested for 18 hours at 37°C in a phosphate-buffered saline solution containing type II collagenase (Worthington, Freehold, NJ; 3 mg/mL), penicillin (200 U/mL), and streptomycin ($200 \text{ } \mu\text{g/mL}$). After the chondrocyte suspension was centrifuged and washed with phosphate-buffered saline solution, the number and viability of the chondrocytes were examined with a hemocytometer and a trypan blue exclusion test.

Autologous Chondrocyte–Calcium Alginate Suspension. The cell pellet was resuspended in 1.8% (wt/vol) sterile liquid sodium alginate (Sigma Chemical Co, St Louis, Mo) to yield a cellular density of 10×10^6 cells per milliliter. The chondrocyte–sodium alginate suspension was kept at 32°C . Just before injection, 200-mmol/L sterilized calcium sulfate was added to the suspension for alginate polymerization. For simultaneous application of the alginate–chondrocyte mixture and calcium sulfate, we used a Pantaject application set (Behring, Marburg, Germany) for the combined application of fibrinogen and thrombin solution to make the physiologic glue Beriplast. Two syringes filled with the alginate–chondrocyte mixture and the calcium sulfate solution were connected to a Y-piece that was applied to a 23-gauge needle, and the contents were injected simultaneously (Fig 1). We always injected 2 mL of the sodium alginate–chondrocyte suspension and 1 mL of calcium sulfate to make a constant injection volume of 3 mL.

Experimental Study. A total of 12 rabbits were injected with their own autogenous chondrocyte–calcium alginate solution (Fig 1). The injection site was the right gluteus muscle. Specimens were harvested at 4 ($n = 6$) or 20 ($n = 6$) weeks after injection. By standard histochemical techniques, serial sections were stained with hematoxylin and eosin, Alcian blue, and Masson's trichrome solution. The specimens were analyzed by a pathologist blinded to the identity of each specimen. The total volume of the harvested tissue was determined by measuring water displacement after the sample was added to a fixed volume, which then was compared with the initial injected volume.

RESULTS

There were $3.7 \pm 0.5 \times 10^7$ chondrocytes isolated per cartilage, with a mean viability of $90.2\% \pm 8.8\%$. All animals tolerated the implantation well, and there was no wound infection. The recovered tissue-engineered cartilages were found to have adherent fibrous capsules. The external appearance was firm but flexible, with an often-irregular pearl-white surface (Fig 2). Because all constructs were delivered by means of injection, the shapes varied over a wide range as determined by the initial injection. Although the initial shape varied, the specimens retained the shape initially defined when the calcium alginate gelled. Overall, tissue-engineered cartilage was generated in 10 of the 12 implants (83%). One of the 2 failed implants was found in the short-term group, and the other in the long-term group. They showed no cartilage generation and were replaced with a small collection of fibrous tissue.

Histologic analysis of the implant specimens with hematoxylin and eosin stains demonstrated viable chondrocytes within lacunae surrounded by newly synthesized matrix substances. The normal production of proteoglycan and collagen fibers of the matrix was identified by Alcian blue and Masson's trichrome staining, respectively. Tissue-engineered cartilage specimens typically demonstrated a fibrous tissue layer surrounding the cartilage, as well as unique fibrous and vascular ingrowth. Basophilic staining of the calcium alginate was commonly found within the 4-week implantation specimens with an accompanying foreign body giant cell reaction (Fig 3). The 20-week implantation group had less calcium alginate and fewer giant cells than did the 4-week group. Interestingly, all grafts from these two groups showed foci of bone formation. The bony trabeculae included marrow-like cells (Fig 4). The total volume of injected implantation, 3 mL, was maintained until harvest. There was no volumetric difference between the two groups (see Table).

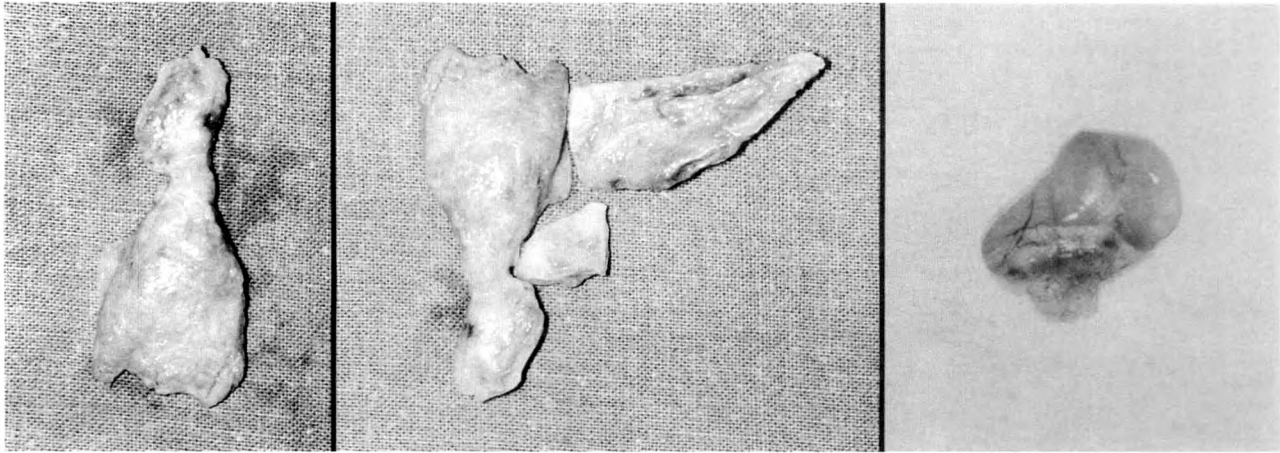


Fig 2. External appearance of harvested grafts. Shapes varied over wide range as determined by initial injection. Consistency was firm but flexible, often with irregular pearl-white surface.

DISCUSSION

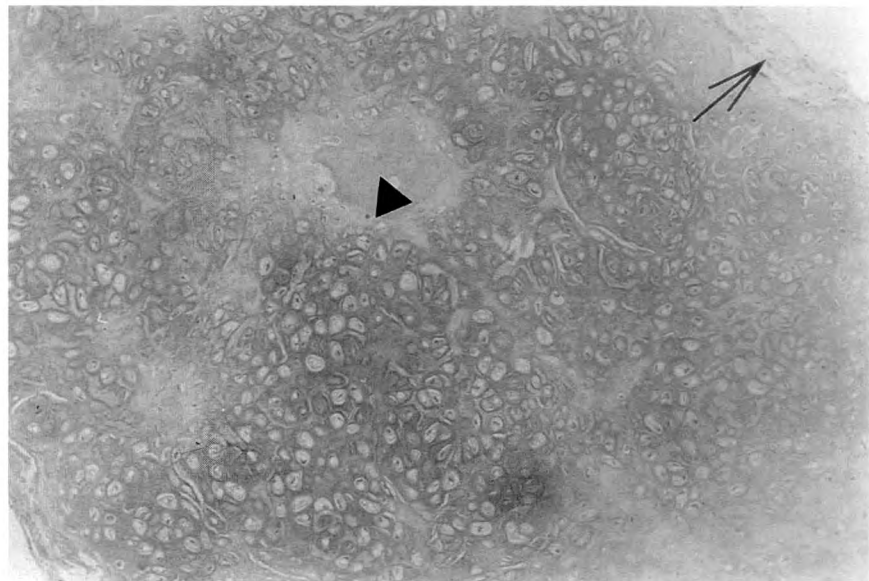
Tissue engineering by cell transplantation with a biodegradable polymer matrix has been proposed by various authors as a new method for achieving organ replacement or creating new tissues. Cartilage generation has been reported *in vivo* and *in vitro*, with systems based on isolated chondrocytes, organic support matrices, and synthetic biodegradable polymer matrices.¹⁻¹⁴ Many authors have shown that calcium alginate can be used to transplant chondrocytes and create neocartilage in animal models. The advantage of this polymerized polysaccharide is that it is nontoxic and injectable.

Calcium alginate is degraded by enzymatic pathways to its two monomeric subunits — glucuronic acid and mannuronic acid — in body tissue.⁹ In the athymic nude mouse model, calcium alginate alone persisted throughout the 12 weeks of *in vivo* incubation and had a doughy consistency without any evi-

dence of cartilage or bone formation. The specimen did exhibit a decrease in mean weight over that period of time that suggested some degradation of the material. The persistence of the alginate may be due to an attenuated inflammatory response because of the altered immune system of the nude mice.^{8,9} Although a control group was not examined in our present study, our preliminary data suggested that 1.8% calcium alginate alone was completely absorbed within 3 months without any scarring in the rabbit model (unpublished data).

In reconstructive or aesthetic surgery, ideal injectable materials to fill soft tissue are needed. Teflon, collagen, and autologous fat have been used for this purpose; however, the migration^{15,16} and re-treatment required have raised concerns as to the use of these materials.¹⁷ The present study was focused on overcoming this limitation by using recently developed cartilage generation techniques.

Fig 3. Tissue-engineered cartilage typically demonstrated surrounding fibrous layer, as well as unique fibrovascular in-growth (arrow; original $\times 40$). There was much basophilic stained calcium alginate, which was not completely absorbed in short-term group (arrowhead).



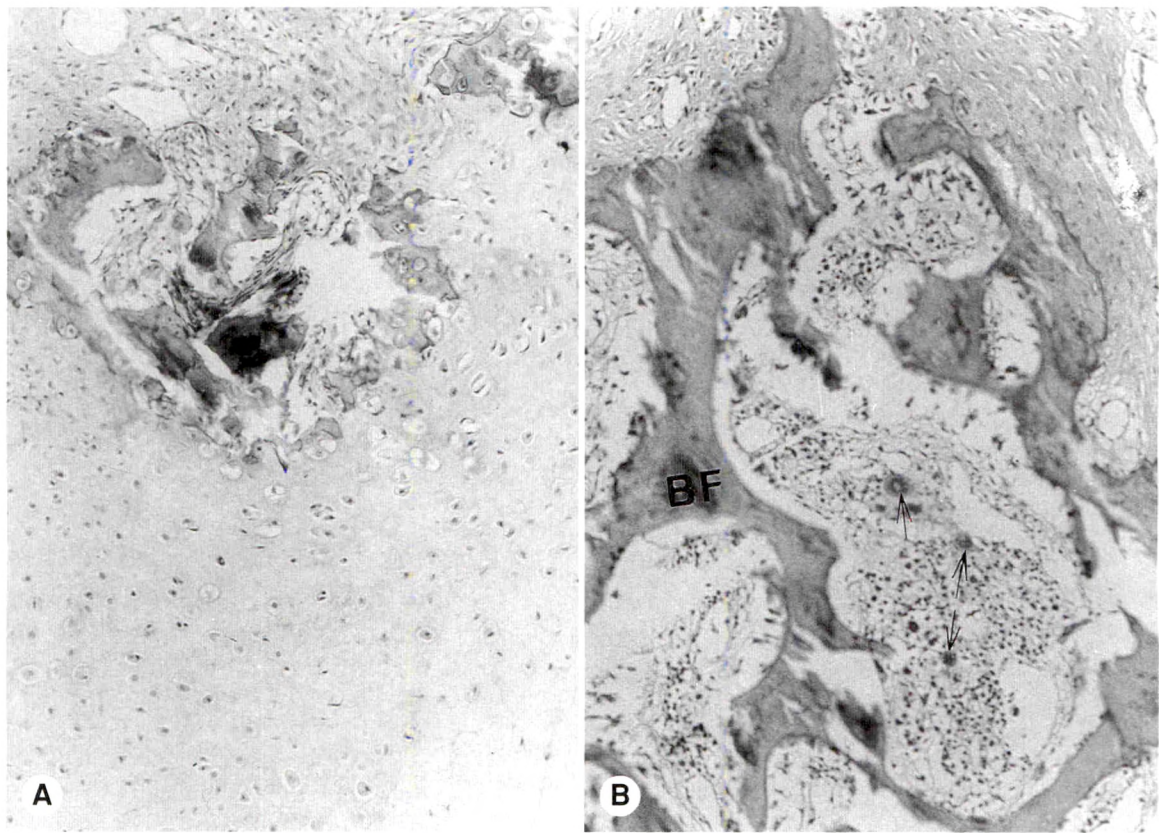


Fig 4. A) All grafts revealed bony foci in vicinity of newly created cartilage (original $\times 100$). B) In high-power field, bone marrow-like cells were noted in bony trabeculae (arrows; original $\times 250$). BF — bony foci.

Most previous reports have dealt primarily with xenograft chondrocyte implantation from a bovine donor to an immune-incompetent murine model.^{1-3,5-9,12,14} These results showed complete replacement of the cartilage. Our results demonstrate that injectable calcium alginate reliably generates cartilage from autogenous chondrocytes in the rabbit model. However, fibrous tissue ingrowth and bone formation were also found. Whether the difference in observations is caused by the use of an immune-incompetent host or a difference in the experimental processing is uncertain. Britt and Park¹³ reported that the autogenous chondrocytes implanted onto a polyglycolic acid–poly-L-lactic acid copolymer template could generate mature cartilage infiltrated by vasculature and fibrous tissue, with delayed osteoid formation in the rabbit model. This result is similar to ours.

EXPERIMENTAL RESULTS OF TWO GROUPS

	4 Weeks (n = 6)	20 Weeks (n = 6)
Cartilage generation (No.)	5	5
Calcium alginate	Noted	Absent
Bony focus formation	All	All
Mean volume of implant (mL; mean $\pm$ SD)	3.2 $\pm$ 0.7	2.9 $\pm$ 0.6*

*Not statistically significant.

From this similar observation, it can be suggested that complete replacement of cartilage occurs only in immune-incompetent mice. Britt and Park further declared that osteoid formation could be observed only in long-term implantation (6 and 12 months). However, in our experiment, all grafts showed bony foci. Therefore, it seems that the bone formation may not depend on the duration of implantation, but on other, unknown causes. They also suggested that the bone formation is caused by vascular infiltration, which may be due to the loss of angiogenesis inhibitor production ability of dedifferentiated chondrocytes. Dedifferentiation of chondrocytes is known to occur when cells are in long-term tissue cultures. We transplanted the chondrocytes without culture processing. Moreover, we previously demonstrated that a third passage of subcultured chondrocytes could create neocartilage without vascular invasion in a nude mouse model.¹⁴ We suspect that the production of angiogenesis inhibitor may be altered by the surrounding inflammatory process or by acute environmental changes, rather than by dedifferentiation.

Despite fibrovascular ingrowth and bone formation, the total injected volume was maintained over 20 weeks. In the specimens from the long-term group, calcium alginate was nearly absent. It seemed that

degraded calcium alginate was replaced by cartilage matrix newly produced from viable chondrocytes. The degradation process of polysaccharide in the living body involves hydrolysis and a foreign body giant cell reaction by macrophages. In the present study, foreign body giant cells appeared more frequently in the short-term group. Tissue macrophages cannot phagocytize any particle larger than 60 μm in diameter. Any alloplastic particles ranging from 20 to 60 μm that have been phagocytized may cause the death of the macrophage with the release of intracellular enzymes. The release of these cytokines results in a local inflammatory response that induces other macrophages to engulf the local debris. However, in the case of biodegradable materials like this alginate, macrophages can hydrolyze this polysaccharide without causing cell death.¹⁸ These findings show promise for soft tissue filling and contour augmentation by means of injection. For clinical application, more long-term study and further studies comparing previous commercially available materials and this au-

togenous chondrocyte–calcium alginate implant are necessary.

In conclusion, this study used autogenous chondrocyte transplants in an immune-competent rabbit model to develop an injectable polymer system useful for cell transplantation and cartilage generation. We demonstrated the following.

1. Chondrocytes can be transplanted successfully by means of injection within a calcium alginate matrix.
2. This in vivo study demonstrated the ability to reliably generate cartilage from autogenous chondrocytes in the rabbit model with injectable calcium alginate.
3. Total replacement of cartilage, however, could not be achieved.
4. Permanent volumetric stability of this graft should be confirmed for clinical application.

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IN VITRO EAR CARTILAGE SHAPING WITH CARBON DIOXIDE LASER

AN EXPERIMENTAL STUDY

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Deformed cartilage remodeling appears to be a challenge, as cartilage tends to keep its initial shape because of internal stresses. Cartilage can be remodeled with heat, and this report describes the use of a CO₂ laser beam for in vitro cartilaginous tissue remodeling. Straight cartilage samples were removed from the ears of 21 rabbits deprived of perichondrium and remodeled with the CO₂ laser at an output power of 3 W, a spot diameter of 2 mm, and an exposure time of 0.5 second. The remodeled cartilages and control samples were implanted into the rabbits' backs and retrieved 6 to 12 months later. Histologic and morphological analysis showed that the irradiated cartilages retained both their shape and their viability. This may be a useful clinical technique for in situ remodeling of a deformed cartilage in operations such as septoplasty.

KEY WORDS — carbon dioxide laser, cartilage shaping, electron microscopy.

INTRODUCTION

Deformity and destruction of facial cartilage resulting from trauma, disease, or ablative surgery provides a difficult reconstructive challenge for the otorhinolaryngologist. The in situ surgical correction of a malformed cartilage is often difficult. Choosing a cartilaginous implant of the appropriate size to replace, augment, or enhance the deficient or deformed areas remains a difficult task. At the same time, giving a new shape to a piece of cartilage is an additional problem because of its tendency to return to its original shape.

In 1993, we proposed a theoretical model, based on mathematical analysis of laser-tissue interaction, suggesting the possible use of a CO₂ laser beam to remodel cartilage into different shapes. Experimental data derived from the exposure of human nasal septum and rabbit ear cartilage to a laser beam confirmed the in vitro feasibility of this technique.¹⁻⁴

In order to measure both the stability of the new shape and the viability of the irradiated cartilage, we irradiated rabbit ear cartilage using defined laser parameters. The cartilage was then implanted subcutaneously in the rabbits' backs. The implants were retrieved after 6 months or 1 year and were studied both morphologically and microscopically.

MATERIALS AND METHODS

Twenty-one rabbits, each weighing less than 1 kg,

were submitted to general anesthesia using ketamine hydrochloride 30 mg × kg⁻¹ and xylazine hydrochloride 5 mg × kg⁻¹. Under sterile conditions, a vertical skin incision was made on the anterior right ear surface. The cartilage was then exposed and a vertical, straight piece of cartilage alone, without its perichondrium (1 × 3 cm), was excised from each animal. The perichondrium was freed from the cartilage and left in situ. Hemostasis was achieved, and the wound was closed with continuous 4/0 chromic catgut suture. Each cartilage sample was divided into 2 pieces. The first one, 2 cm long and 1 cm wide, was irradiated with a CO₂ laser, while the other, 1 cm long and 0.5 cm wide, was used as a control sample. The thickness of all the cartilage pieces was approximately 1 mm. The laser beam was delivered in the central area of only 1 surface in the group of irradiated cartilages, by means of a Sharplan 1040 CO₂ laser at a wavelength of 10.6 μm. The laser beam was focused to the desired spot size with a barium fluoride lens, transparent at 10.6 μm, with a focal length of 400 mm, mounted on a surgical microscope. Intermittent exposures were used, the spot diameter was 2 mm, the exposure time was 0.5 second, and the output power was 3 W. In each exposure the achieved energy was 48 J × cm⁻². Twenty to 30 pulses of 0.5 second or 60 to 90 J were required to remodel each cartilage. These laser parameters were based on the results of our previous experiments.¹ Particular care was taken not to irradiate the same area twice. All of the straight irradiated samples assumed a new per-

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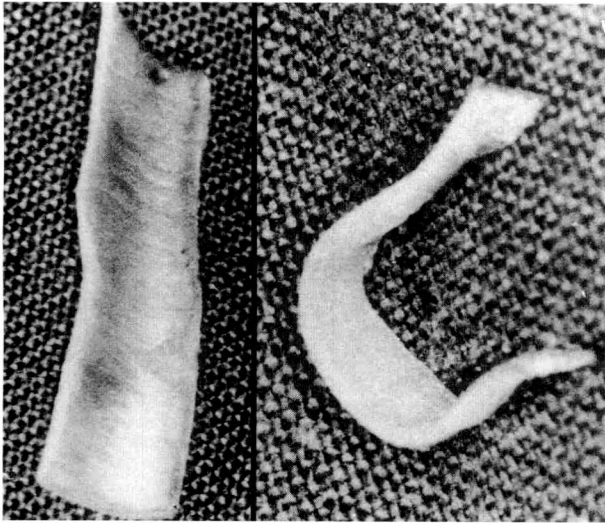


Fig 1. Straight piece of rabbit ear cartilage (left) was transformed and acquired new "U" shape (right) after CO₂ laser treatment of its middle portion.

manent U-shaped curve (Fig 1). Two separate subcutaneous pockets were made in the rabbits' backs, into which the control (left side) and irradiated implants (right side) were placed. The pockets were closed with 3/0 chromic catgut, and 1 million units of procaine penicillin was administered intramuscularly.

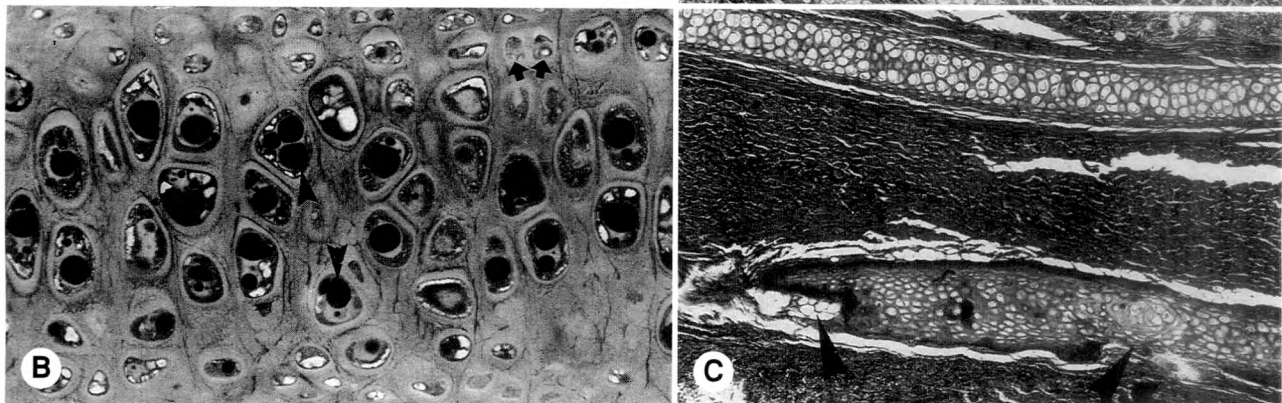
One animal died on the seventh postoperative day for an unknown reason. Ten animals were painlessly sacrificed with intravenous Pentothal after 6 months.

The remaining 10 animals were painlessly sacrificed after 1 year. The paired cartilage implants were removed from the sacrificed animals and examined with light and electron microscopy. The tissue samples were fixed in 2.5% glutaraldehyde in 0.1-mol/L cacodylate buffer (pH 7.4). After 24 hours, the samples were post-fixed in osmium tetroxide in 0.1-mol/L cacodylate buffer for 2 hours at 4°C, dehydrated in a series of alcohols and in propylene oxide, and embedded in epoxy resin for electron microscopy. Samples for light microscopy were embedded in paraffin wax and then stained with van Gieson's trichrome solution, hematoxylin and eosin, and Alcian blue. The epoxy resin-embedded samples were cut into sections 1 to 3 mm thick and stained with toluidine blue for light microscopy. Selected areas were then cut into thin sections and stained with uranyl acetate and lead citrate for electron microscopy. Imaging was carried out with a JEM 100CX electron microscope.

RESULTS

Light Microscopy. Six months after irradiation, all cartilage samples retained their new shape and were surrounded by dense connective tissue. There was very little evidence of inflammation (Fig 2A). Optical microscopy showed that the cartilage cells were viable and functioning. At the periphery of the graft, there were obvious mitoses (Fig 2B). It was not clear whether these were in chondrocytes that had been reactivated, or in fibroblasts derived from the sur-

Fig 2. Rabbit ear cartilage, 6 months after laser treatment, embedded in paraffin and stained with van Gieson's trichrome solution. A) Irradiated area (between arrows) retained its new shape (original $\times 100$). B) Fragment of A (original $\times 500$). Cells at graft's periphery (arrows), possibly under multiplication. Fat droplets (arrowheads) inside chondrocytes of central cartilage portion. C) More pronounced cartilage destruction in nonirradiated edge of cartilage (arrowheads) compared with A (original $\times 100$).



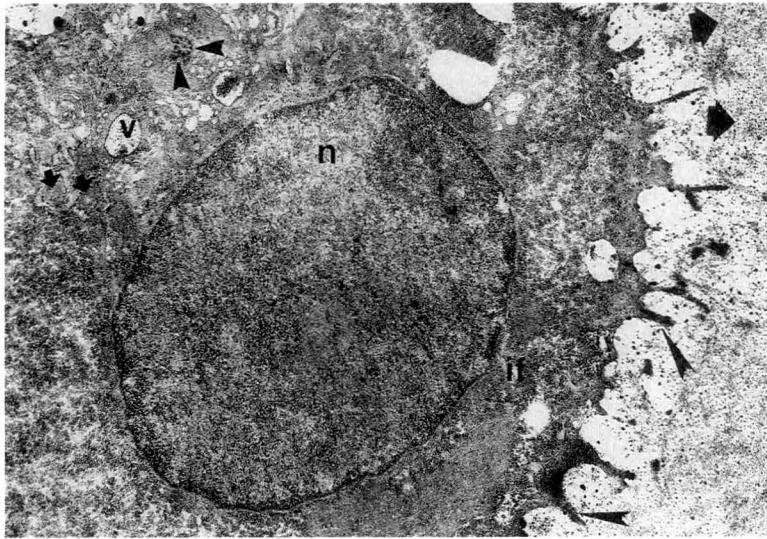


Fig 3. Chondrocyte from irradiated area, 8 months after laser treatment (original $\times 10,000$). Most cells are viable, and cell organoids have normal appearance: nucleus (n), mitochondria (small arrows), vesicles (v), microvilli (large arrowheads), centrioles (small arrowheads), intermediate filaments (if), and collagen fibers (large arrows).

rounding connective tissue. An interesting finding was that the replacement of cartilage by fibrous tissue was more pronounced in the nonirradiated specimens than in the irradiated ones. Replacement occurred around the periphery of the samples, while the cartilaginous structure in the irradiated area remained intact (Fig 2C).

Electron Microscopy. Fat cell differentiation was revealed in some parts of the irradiated specimens and was more pronounced in the central area of the samples. Some of these cells had only a thin rim of cytoplasm surrounding the lipid masses. The presence of endoplasmic fat droplets is more characteristic of elastic cartilage than of hyaline cartilage, but the cells seen were, apart from this feature, much more typical of those seen in hyaline cartilage. There was evidence of normal cellular function in that cells contained large central nuclei and appeared to possess functioning endoplasmic reticulum, Golgi apparatus, normal-looking mitochondria, and a normal membrane and vesicles (Fig 3A). A large number of

filaments was observed beneath the external membrane of the chondrocytes, as well as numerous intermediate filaments in the vicinity of the nucleus. This finding is typical of elastic cartilage cells. There were numerous invaginations, protrusions, and microvilli on the chondrocyte surface itself. The observation of newly replicated centriole pairs within the chondrocytes in the irradiated areas revealed a division in some of them (Fig 3B).

Fibroblast-like cells were found toward the periphery of the specimens (Fig 4A). These were either fibroblasts that had migrated in from the fibrous tissue surrounding the graft, or differentiating graft chondrocytes migrating outward. The collagen surrounding these cells had thicker fibrils than those found in the intact matrix of the irradiated specimens (Fig 4B).

Late Results. After 1 year, the number of dead cells and degenerating cells was increased (Fig 5). Areas of calcification were present in the irradiated areas in 3 of the 10 cartilages. The vast majority of the

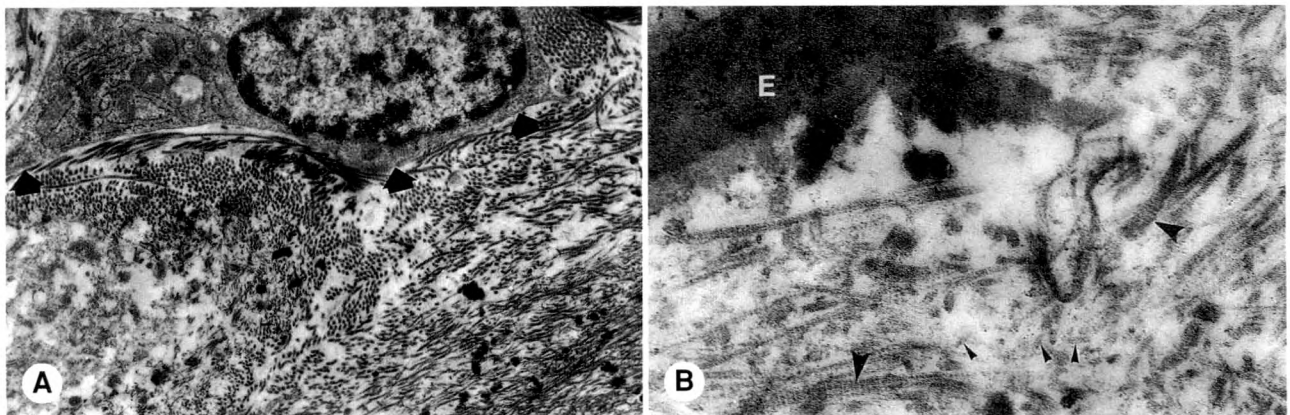


Fig 4. Irradiated cartilage, 8 months after laser treatment. A) Fibroblast-like cell (arrows) from graft's periphery (original $\times 2,600$). B) Fragment of A (original $\times 8,000$). Cell is surrounded by collagen fibers (large arrowheads) of different thickness and spatial orientation than fibers of intact ear cartilage (small arrowheads). E — elastic fibers.

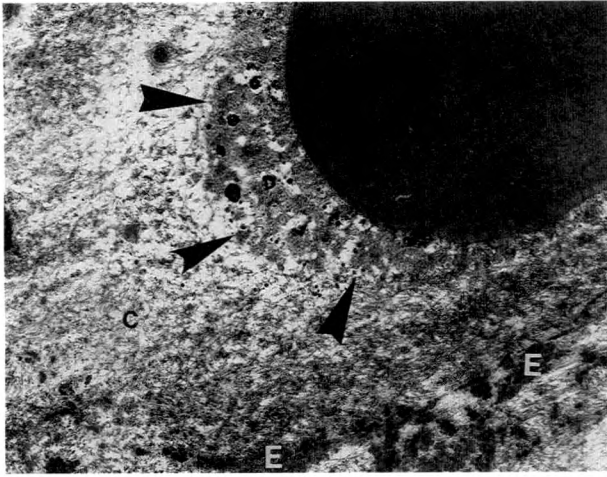


Fig 5. Irradiated cartilage (original $\times 5,000$). Collagen fibers (c) and remnants of chondrocytes (between arrowheads) 12 months after irradiation. E — elastic fibers.

irradiated chondrocytes were still alive after 1 year, but the number of empty lacunae and the number of chondrocytes exhibiting fatty degeneration had increased. All 10 irradiated samples had retained their new shape.

DISCUSSION

Cartilage remodeling has been the subject of extensive study in the past. Gibson and Davis⁵ first described the presence of interlocking stresses in human costal cartilage, and Fry⁶⁻⁸ studied the same phenomenon in human nasal septal cartilage. Fry showed that a series of partial thickness incisions on an intact cartilage surface released the tension and allowed the cartilage to bow away from the incised surface. Rubin⁹ proposed the use of an instrument that produced multiple penetrating incisions through cartilage in order to neutralize the interlocking stress forces. Thomas¹⁰ showed that the intravenous injection of papain into young rabbits caused the ears to change their shape within 4 hours; the cartilage hardened and returned to its original shape within 3 to 5 days. De Palma et al¹¹ demonstrated that the immersion of rabbit ear cartilage in normal saline solution allowed the introduction of deformities that remained fixed for up to 8 days after the cartilage had been reimplanted into the anterior abdominal wall. Many other methods, including cross-hatching, carving, crushing, thinning, excising, and repositioning the cartilage, have been used in order to obtain satisfactory remodeling.

The mechanism proposed for laser beam effect on cartilage involves heat application to the proteoglycan component of the cartilage matrix. Total or partial damage to the protein components of the proteoglycans by laser energy may destroy their water-binding ability and thereby lead to an uneven reduction

in the tensile stress within the cartilage, resulting in a remodeling effect. This hypothesis is supported by both light and electron microscope studies.⁷ The proteoglycans form the matrix component of the cartilage; they are responsible for setting up tensile stresses on collagen "anchor points," resulting in the expansion of the collagen framework.⁷ Our recent studies showed that the distortion of proteoglycans after laser exposure, as shown in electron microscopy, resulted in collagen skeleton alterations as compared with control specimens. More specifically, 1) in the plane of histologic section, many collagen fibers appeared shorter than normal; 2) the number of ring-shaped collagen components was significantly increased; and 3) the collagen fibers, which normally have a symmetric orientation, especially around the borders of the "chondrocyte nests," as well as in the vicinity of the perichondrium, lost their spatial orientation in the irradiated areas. Orientation became more random, resulting in a homogeneous appearance of the matrix.⁴

The permanent remodeling of a cartilage implant that is destined to serve as a framework for the reconstruction of traumatized or deformed areas of a tissue continues to pose problems. Use of alloplastic grafts seemed to be promising, but it was associated with an unacceptable level of complications such as infection, graft extrusion, and necrosis of subjacent normal tissue. Many surgeons have therefore turned back to the less pliant but more reliable homologous or autologous cartilage graft.¹²

Cartilage homografts can usually provide the required amount of cartilage, but they often need to be carved to assume an appropriate shape. Unfortunately, current homograft preservation methods, commonly making use of chemical antimicrobial agents, tend to lead to chondrocyte death. The resulting non-viable graft is associated with a significantly higher incidence of absorption, resorption, and ossification than are autografts.^{13,14} Autografts are therefore the most commonly used source of material, although their small size often requires more than one donor site and therefore a prolonged operative time.¹⁵ When an autograft of a particular shape is needed, the surgeon has to resort to one or another of the physical methods outlined above to shape it, and these methods often lead to an undesirable loss of cartilage rigidity and a failure to keep the desired shape. Laser remodeling is a technique whereby the living cartilage is altered by heat and remains viable afterward.

The observation that treated cartilage is well tolerated, keeps its shape without provoking inflammation in surrounded tissue, and remains viable without evidence of resorption after 6 to 12 months dem-

onstrates the potential efficacy of our technique for reconstructive surgery. It is also notable that the cartilage assumes some elastic properties and is incorporated into the host tissue by means of a fibrous re-action.

This experimental work paves the way for further basic and clinical research. We are currently investi-

gating the strength of irradiated, reshaped, and reimplanted cartilage. We are also looking at the effect of a laser beam on cartilage that has been previously treated with hyaluronidase or collagenase; these selectively destroy the proteoglycan or collagen framework of the cartilage. At the same time, we have performed laser remodeling in selected cases of nasal cartilage deformity.

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CORRECTION

An error appears in an author's name in "Artifactual Thickening of the Sinus Walls on Computed Tomography: A Phantom Model and Clinical Study" (Sichel et al, *Ann Otol Rhinol Laryngol* 2000;109:859-62). The fourth author should be listed as Fatma Gul Aksoy, MD, rather than Fatma Gul-Aksoy, MD. The author's surname is Aksoy.

IMAGING CASE STUDY OF THE MONTH

CONGENITAL INTERNAL CAROTID ARTERY ANEURYSM WITH ABSENCE OF THE PETROUS PORTION OF THE CONTRALATERAL INTERNAL CAROTID ARTERY

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INTRODUCTION

Infrequently, the carotid artery may present aberrantly in the middle ear. This may be the consequence of an injury or infection that leads to erosion of the medial wall of the carotid canal, or it may be the consequence of a congenital anomaly or an aneurysm. Aneurysms of the internal carotid artery are rare, especially in the petrous region.¹ We present a case of an internal carotid artery aneurysm involving the high cervical, petrous, and cavernous portions of the artery, with absence of the petrous portion of the contralateral internal carotid artery.

CASE REPORT

A 10-year-old boy was referred to the senior author (P.S.R.) for evaluation of right-sided hearing loss, which had been noted when he failed his school audiogram. The referring physician had noted a middle ear mass. No symptoms of vertigo, tinnitus, or otorrhea were elicited. The patient's medical history was notable for tetralogy of Fallot, for which he had undergone surgery. Physical examination revealed a normal right external auditory canal and a white mass behind the tympanic membrane in the anterior inferior quadrant. The posterior portion of the tympanic membrane was retracted, atelectatic, and thinned. An audiogram revealed a 60-dB air-bone gap in the right ear, with normal thresholds in the left ear.

The patient was taken to the operating room for exploratory tympanotomy. Upon elevation of the tympanomeatal flap, a thick, white mass was noted filling the entire inferior hypotympanum and a large portion of the anterior mesotympanum. Aspiration of the mass with a 22-gauge needle revealed red, pulsatile blood flow. Because the mass was suspected of being an aberrant carotid artery, the tympanomeatal

flap was replaced into position and the procedure terminated.

Axial and coronal thin-section computed tomographic scans were obtained through the temporal bone the following day. Massive dilation of the right carotid canal was noted (Fig 1). Heavily weighted T2 fast-spin echo sequences were obtained in the axial and coronal planes through the brain and temporal bone. A standard magnetic resonance angiogram was also obtained at this time. A large saccular aneurysm of the right carotid artery involving the high cervical, horizontal, and cavernous portions was noted (Fig 2).

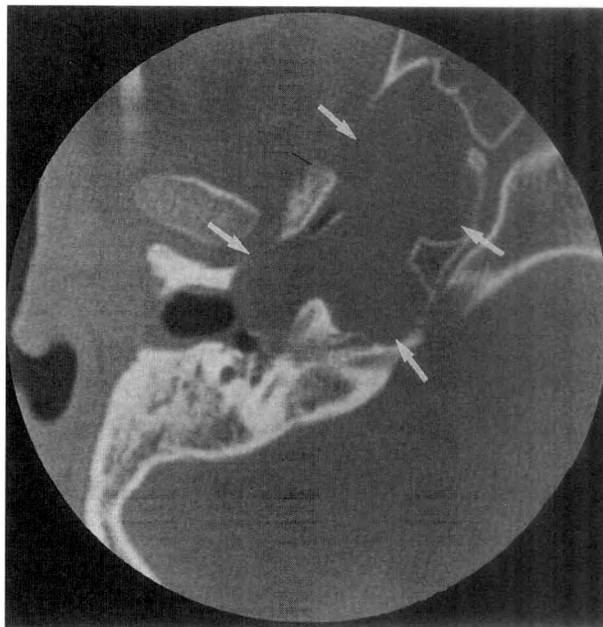


Fig 1. Axial computed tomographic scan through temporal bone. Arrows indicate massively dilated carotid canal.

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Fig 2. Axial maximum-intensity projection from 3-dimensional time-of-flight magnetic resonance angiogram shows large saccular aneurysm.

An arteriogram was obtained to better delineate the vascular abnormalities seen on the magnetic resonance angiogram. Again, the large saccular aneurysm involving the high cervical, petrous, and cavernous portions of the right internal carotid artery was demonstrated. The left middle cerebral artery and right posterior communicating artery were noted to arise from the aneurysm. The petrous portion of the carotid artery was noted to be ectatic, and the lateral wall of the internal carotid artery was dehiscant into the middle ear (Fig 3). The right vertebral artery was noted to be hypoplastic. The cervical and petrous portions of the left internal carotid artery were absent, with collateral vessels between the cavernous portion of the left internal carotid artery and the left internal maxillary artery and middle meningeal arteries. The left vertebral artery was noted to be supplying the left parieto-occipital region, as well as the left middle cerebral artery distribution (Fig 4).

DISCUSSION

Aneurysms of the internal carotid artery are rare, especially in the petrous portion. Sahs et al¹ reviewed 3,000 cases of internal carotid artery aneurysms and found none in this region. Sinnreich et al² had the largest series in the literature, reporting 23 aneurysms of the petrous portion of the internal carotid artery.

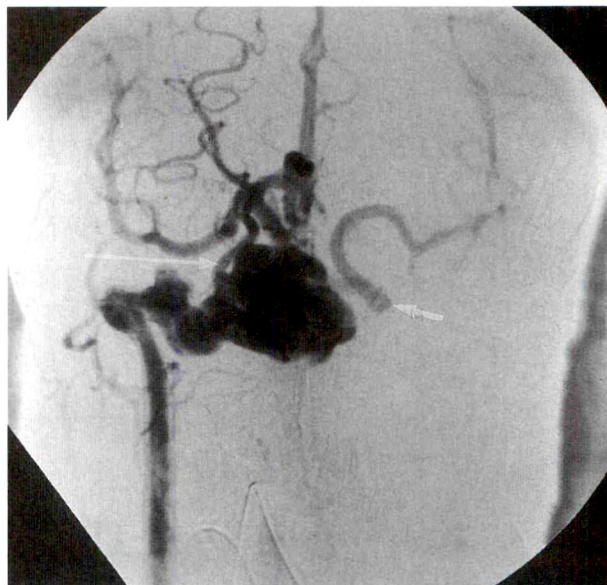


Fig 3. Anteroposterior view during injection of right internal carotid artery (ICA). Large saccular aneurysm of right ICA is seen, which bulges into suprasellar cistern. Left middle cerebral artery (short arrow) arises from aneurysm, as does right posterior communicating artery (long arrow). Petrous portion of carotid artery is ectatic, and lateral wall of ICA is dehiscant into middle ear.

Most aneurysms are congenital, but infection, cholesteatoma, or trauma may cause dehiscence of the bone that overlies the carotid artery in the petrous region.³⁻⁵ Congenital aneurysms usually occur at sites in which vessel walls are weak, such as the region in which primordial vessels involute or in a region in which the vessel makes a sharp turn, such as the petrous portion of the carotid artery.^{2,6}

There are many reports in the literature of hemor-

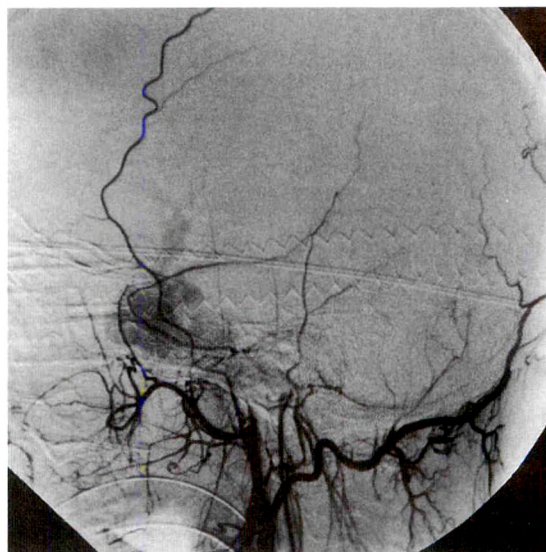


Fig 4. Lateral view during injection of left common carotid artery. Left ICA is occluded. Dilation of branches of left external carotid artery and some filling of aneurysm through arterial collaterals are seen.

rhage or central sequelae resulting from biopsy of the carotid artery in the middle ear.^{2,7,8} Tympanometry can positively identify a vascular lesion by revealing pulsations synchronous with the heartbeat or by a positive Brown's sign.⁹ Differentiating between a glomus tumor and an aberrant carotid artery is not possible with tympanometry — it requires arteriography. During surgery, an aberrant carotid artery can be diagnosed by aspirating the vessel with a 27-gauge needle and sending the specimen for blood gas analysis.¹⁰

An aberrant carotid artery may be diagnosed on a high-resolution computed tomographic scan if one of the following is seen: an absent vertical segment of the internal carotid artery; dehiscence of the bone overlying the carotid artery in the tympanic segment; an enhancing hypotympanic mass, or an enlarged inferior tympanic canaliculus.³ Lapayowker et al¹¹ reported that if the carotid artery can be seen lateral to the vestibule on frontal projections, an aberrant position should be suspected.

A magnetic resonance angiogram provides excellent visualization of the carotid artery in most cases, yet has lower resolution than a conventional angiogram.^{12,13} The noninvasiveness of this imaging meth-

od makes it useful in evaluating children.

The treatment of internal carotid artery aneurysms in the petrous portion of the canal is variable. In asymptomatic patients, balloon occlusion testing may be performed to assess the risk of neurologic sequelae with ligation of the artery.¹⁴ In patients who do not tolerate balloon occlusion, bypass surgery may be performed.

Neither bypass surgery nor ligation was a viable option for our patient, who had absent cervical and petrous portions of the contralateral carotid artery and a hypoplastic right vertebral artery. To our knowledge, this constellation of anomalies has never been reported before.

CONCLUSION

Aneurysms of the petrous portion of the internal carotid artery are rare causes of middle ear masses. We report a case of a patient with a large aneurysm involving the petrous and cavernous portions of the carotid artery with absent cervical and petrous portions of the contralateral carotid artery. When an aneurysm of the petrous portion of the internal carotid artery is suspected, magnetic resonance angiography or traditional angiography should be performed to confirm the diagnosis.

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CLINICOPATHOLOGICAL CONSULTATION

PATHOLOGICAL FEATURES OF LYMPHOID PROLIFERATIONS OF THE SALIVARY GLANDS: LYMPHOEPITHELIAL SIALADENITIS VERSUS LOW-GRADE B-CELL LYMPHOMA OF THE MALT TYPE

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Lymphoid proliferations of the salivary glands can be either reactive or neoplastic. Reactive lesions include the lymphoepithelial sialadenitis (LESA; also known as myoepithelial sialadenitis [MESA]) of Sjögren's syndrome. Lymphomas of the salivary glands are predominantly B-cell type and include extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type. The spectrum of histopathologic features of LESA/MESA includes 1) "fully benign lymphoid infiltrate," with or without an associated lymphoid follicular structure, without immunoglobulin (Ig) light chain restriction in B-cells, and without any features of aggressive behavior, and 2) "lymphoproliferative lesions," with or without areas of Ig light chain restriction in B-cells, with the usual presence of centrocyte-like cells. A more or less pronounced lymphoepithelial aggressiveness may be present without definite evidence of malignancy. B-cell clones are detected in over 50% of cases of LESA/MESA by molecular genetic methods, but this does not correlate with morphological or clinical evidence of overt lymphoma. On the other hand, "marginal zone B-cell lymphoma of the MALT type" of the salivary glands produces a dense lymphoid infiltrate diffusely involving the gland, with obliteration of acini. The centrocyte-like cells form broad "halos" around the epithelial cell nests and broad strands between lymphoepithelial lesions, often linking together several lymphoepithelial lesions. Further, lymphoma cells express monotypic surface Ig, and in the majority of the cases, the plasma cells are also monoclonal. In conclusion, the diagnosis of LESA/MESA versus marginal zone B-cell lymphoma of the MALT type still relies on the evaluation of morphological features. It seems that molecular genetic analysis has little or no practical role in the clinical diagnosis of salivary gland lymphoma in a setting of LESA/MESA and Sjögren's syndrome.

INTRODUCTION

Lymphoid proliferations of the salivary glands can be either reactive or neoplastic. Reactive lesions include lymphoepithelial sialadenitis and cystic lymphoid hyperplasia, which is a multicystic ductal proliferation with reactive germinal centers, most often seen in intravenous drug users infected with human immunodeficiency virus.¹⁻³

Lymphoepithelial sialadenitis (LESA), also known as myoepithelial sialadenitis (MESA), may be associated with Sjögren's syndrome (SS) or with other connective tissue diseases, particularly rheumatoid arthritis. It may also occur as isolated salivary gland enlargements in patients without other associated diseases.⁴

A variety of terms have been used for LESA and SS. In 1952, Godwin⁵ suggested that the pathological lesions of what had come to be called Mikulicz's disease were represented by lymphoid proliferations of the salivary glands consisting of lymphoid hyperplasia and epithelial alterations. He coined the term

"benign lymphoepithelial lesion." In 1953, Morgan and Castleman⁶ provided the first description of the characteristic altered salivary ducts, to which they gave the name epimyoeplithelial islands because of the belief that both epithelial and myoeplithelial cells were present. The term MESA was later introduced for the histopathologic lesion.⁷

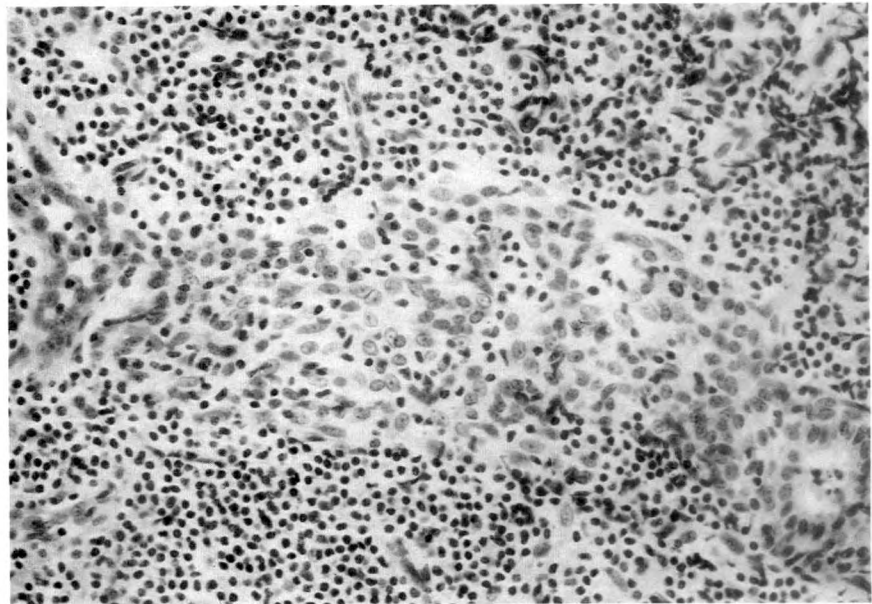
However, it is now known that the nonlymphoid cells involved in these lesions are not myoeplithelial cells, but rather, basal epithelial cells. The term lymphoepithelial lesion is now widely used to refer to the structures produced by marginal zone and/or monocytoid B-cells surrounding and infiltrating the epithelium in normal mucosa-associated lymphoid tissue (MALT) or in MALT-type lymphoma of other sites. Therefore, it seems reasonable in this review to use the term lymphoepithelial lesion (Fig 1). Further, the term LESA/MESA will be used to encompass patients with SS, all of whom have LESA/MESA, and patients with LESA/MESA without SS.

Non-Hodgkin's lymphomas (NHLs) of the sali-

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Fig 1. Microphotograph shows typical lymphoepithelial lesion (H & E, original $\times 250$). Lymphoid infiltrate surrounding and infiltrating salivary ducts is associated with disorganization and proliferation of ductal epithelial cells.



vary glands are predominantly B-cell type. According to the terminology of the revised European-American classification of lymphoid neoplasms (REAL),⁸ NHLs of the salivary glands mainly include marginal zone B-cell lymphoma of the MALT type and B-cell diffuse large cell lymphomas. B-cell diffuse large cell lymphomas may be either MALT-derived or “transformed,” that is, originating from a follicular lymphoma. Other nodal-type lymphomas, such as follicular lymphoma, peripheral T-cell lymphoma, and Burkitt’s lymphoma, may also occur.⁴

This review deals with a detailed characterization of LESA/MESA and low-grade marginal zone B-cell lymphoma of the MALT type of the salivary glands and focuses on the specific pathological features of these disorders.

LESA/MESA

Among all the lymphoma subtypes, the critical point is how to distinguish LESA/MESA from low-grade B-cell lymphoma of the MALT type. This distinction is required for epidemiological, clinical, and pathological reasons.

First, the salivary gland infiltrate known as LESA/MESA is present in virtually all patients who fit the clinical definition of SS. This is very important, because patients with LESA/MESA have a 44-fold increased risk of developing salivary gland or extra-salivary lymphomas.⁹ Notably, most of them are marginal zone B-cell lymphomas of the MALT type.^{7,10,11} Further, the histopathologic features of LESA/MESA may range from clearly benign lymphoid infiltrates to lesions that can be difficult to differentiate from low-grade NHL.^{11,12}

The spectrum of histopathologic features of LESA/MESA includes 2 different patterns, for which the terms “fully benign lymphoid infiltrate” and “lymphoproliferative lesions”¹² have been proposed.

In the histopathologic pattern termed “fully benign lymphoid infiltrate,” the lobular architecture of the gland is preserved (Fig 2A), lymphoepithelial lesions are prominent, and monocytoid and/or marginal zone B-cells (centrocyte-like [CC-L] cells) are restricted to the lymphoepithelial lesions (Fig 2B). In addition to the features already mentioned, most cases of LESA/MESA with “fully benign lymphoid infiltrate” also display prominent reactive follicles without expansion of the mantle or marginal zones (Fig 2C) and display small lymphocytes and plasma cells (rarely in broad sheets) in the interfollicular regions (Table 1).

In the second histopathologic pattern of LESA/MESA, termed “lymphoproliferative lesions,” the process is diffuse or multifocal within the gland, islands of normal acini are often preserved, and aggregates of CC-L cells may be present within the diffuse lymphoid infiltrate (Fig 3).^{4,13} The last feature is crucial, because whether CC-L cells are present as an aggregate or form broad strands marks the difference between reactive and neoplastic lymphoproliferations, respectively.^{4,7,11,13} Observing Fig 3, one can realize how difficult the differential diagnosis between LESA/MESA and low-grade marginal zone B-cell lymphoma of the MALT type may be. Further, it should not be forgotten that in cases of LESA/MESA with “lymphoproliferative lesions,” lymphoepithelial aggressiveness may sometimes be pronounced and areas of immunoglobulin (Ig) light chain restriction may be present (Table 2). In cases displaying these

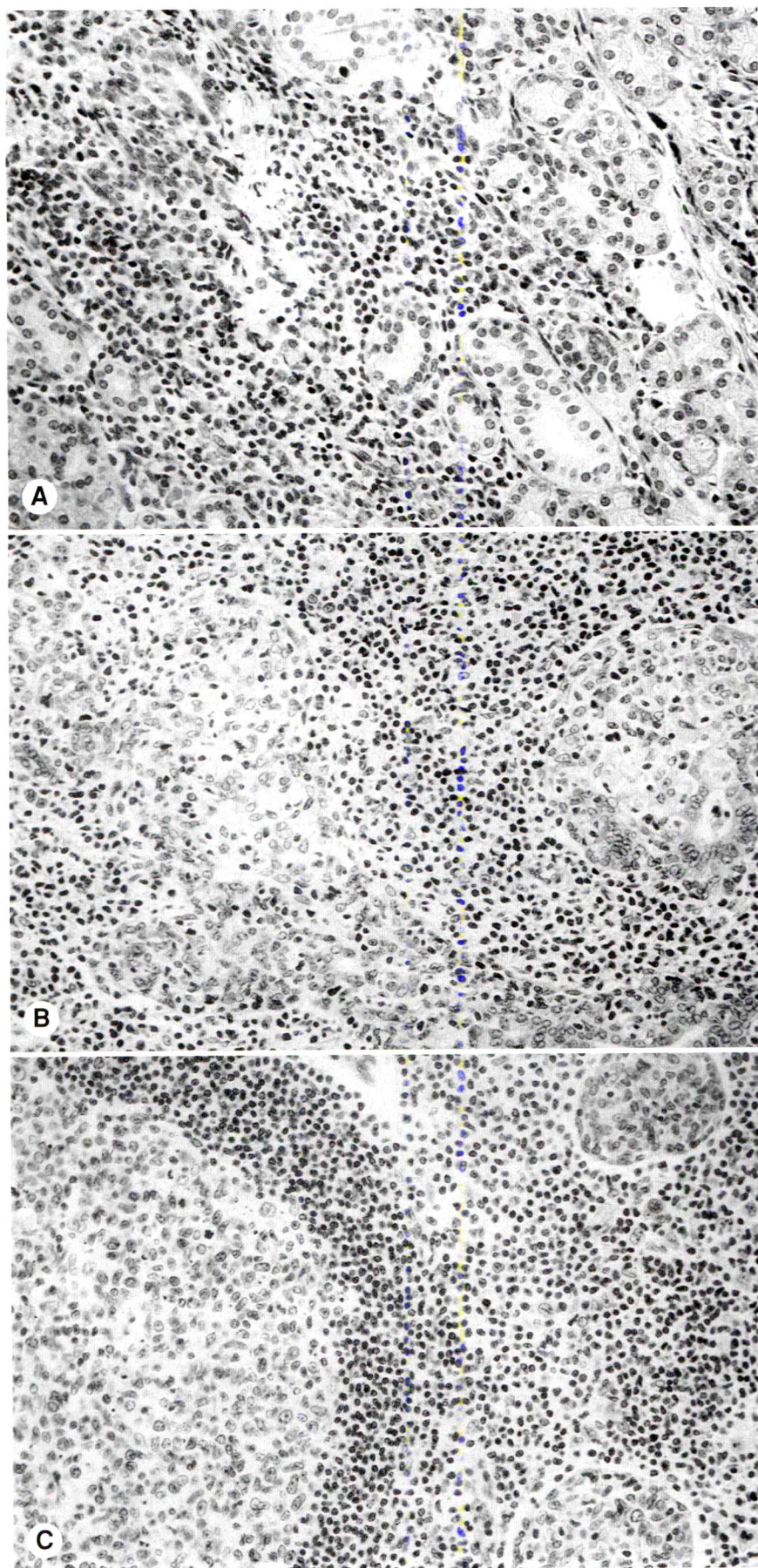


Fig 2. Lymphoepithelial sialadenitis with "fully benign lymphoid infiltrate" (H & E, original $\times 250$). A) Lobular architecture of gland is preserved. B) Centrocyte-like cells are present within, but not around, epithelium. C) Reactive lymphoid follicle displays large germinal center (on left). It does not show expansion of mantle or marginal zones. Lymphoepithelial lesions are also present (on right).

TABLE 1. HISTOPATHOLOGIC FEATURES OF LESA/MESA WITH "FULLY BENIGN LYMPHOID INFILTRATE"

Lobular architecture of gland is preserved
Lymphoepithelial lesions are prominent
Monocytoid and/or marginal zone B-cells (centrocyte-like) are restricted to lymphoepithelial lesions
Reactive follicles without expansion of mantle or marginal zones are prominent
Small lymphocytes and plasma cells (usually not in broad sheets) are present in interfollicular regions
LESA/MESA — lymphoepithelial sialadenitis/myoepithelial sialadenitis.

features, the differential diagnosis between LESA/MESA and low-grade marginal zone B-cell lymphoma of the MALT type may be very difficult. In these cases, monotypic surface Ig expression detected by immunohistochemistry and morphological demonstration of broad strands of CC-L cells are essential features in supporting a diagnosis of NHL.^{4,7,11,13,14} (See below for the complete diagnostic criteria for low-grade marginal zone B-cell lymphoma of the MALT type.)

MONOCLONAL LYMPHOPROLIFERATIVE DISEASE OF UNCERTAIN SIGNIFICANCE

In contrast to the immunohistochemical detection of monoclonality by Ig light chain expression, detection of B-cell clones by Southern blot or polymerase chain reaction (PCR) analysis of Ig gene rearrangement has not proved to be a reliable predictor of clinical behavior in LESA/MESA.

Expansion of B-cell clones is an early event in the course of LESA/MESA. By molecular genetic methods, B-cell clones are detected in over 50% of cases

TABLE 2. HISTOPATHOLOGIC FEATURES OF LESA/MESA WITH "LYMPHOPROLIFERATIVE LESIONS"

Process is diffuse or multifocal within gland
Islands of normal acini are often preserved
Aggregates of centrocyte-like cells are present within diffuse lymphoid infiltrate
Lymphoepithelial aggressiveness may be pronounced
Areas of immunoglobulin light chain restriction may be present

of LESA/MESA.^{13,15,16} Persistent clones may transform into malignant lymphomas, but the frequency of transformation is still unknown.¹⁷ Therefore, the term "monoclonal lymphoproliferative disease of undetermined significance" (MLDUS) has been proposed for these monoclonal lymphoproliferations.¹⁷

According to pathological and molecular data, these lymphoproliferative disorders are limited in extent, are composed of small lymphocytes, and show Ig gene rearrangement. Further, according to our own experience¹² and the recent literature,^{13,15,16} the detection of B-cell clones in cases of LESA/MESA by molecular genetic methods does not correlate with morphological or clinical evidence of overt lymphoma. Therefore, we suggest keeping this kind of monoclonal lymphoproliferation within the LESA/MESA group, but as a provisional subgroup. On these bases, the spectrum of lymphoid proliferations associated with LESA/MESA includes "fully benign lymphoid infiltrate," "lymphoproliferative lesions," and "MLDUS" when, in either histopathologic pattern, B-cell clones are detected by molecular genetic methods (Table 3).

No specific treatment is recommended for lymphoid proliferations associated with LESA/MESA.

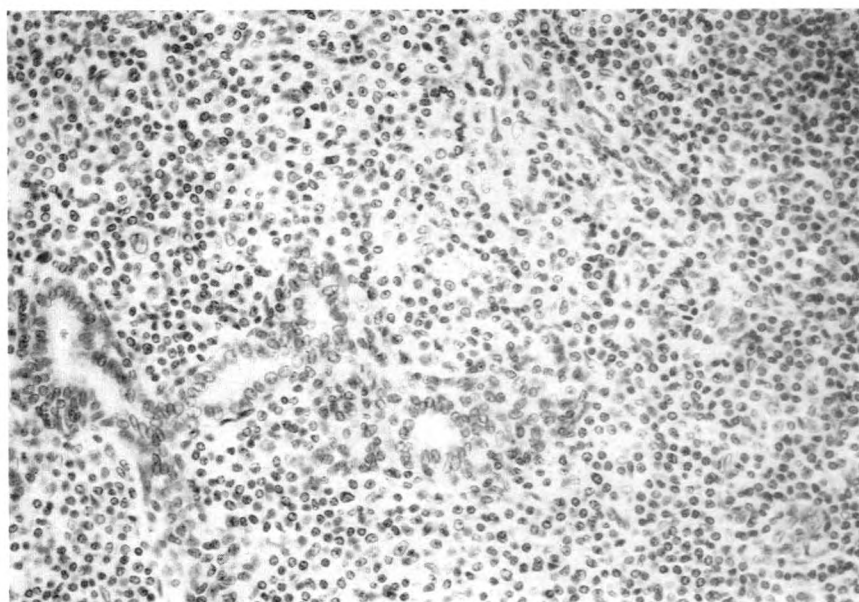


Fig 3. Lymphoepithelial sialadenitis with "lymphoproliferative lesion" (H & E, original $\times 250$). Centrocyte-like cells can be seen at center of field.

TABLE 3. SPECTRUM OF LYMPHOID PROLIFERATIONS ASSOCIATED WITH LESA/MESA

"Fully benign lymphoid infiltrate"	↙	"MLDUS"
"Lymphoproliferative lesion"	↘	

MLDUS — monoclonal lymphoproliferative disease of undetermined significance. Arrows indicate that MLDUS may be detected in both histopathologic patterns by molecular genetic methods.

However, since the ultimate behavior of these lesions remains unknown, close follow-up with rebiopsy of any persistent or recurrent mass lesions is advised, as LESA/MESA-associated lymphoid proliferations can progress or transform over time.¹³

MARGINAL ZONE B-CELL LYMPHOMA OF MALT TYPE

As reported in Table 4, in marginal zone B-cell lymphoma of the MALT type of the salivary glands, a dense lymphoid infiltrate, with obliteration of acini, diffusely involves the gland or may form a localized mass. Lymphoid cells express monotypic surface Ig, plasma cells are also monoclonal, and a high-grade component is detectable.

Both in marginal zone B-cell lymphoma of the MALT type of the salivary glands and in LESA/MESA, reactive lymphoid follicles and lymphoepithelial lesions are usually prominent, whereas only in marginal zone B-cell lymphoma of the MALT type, but not in LESA/MESA, CC-L cells form broad "halos" around the epithelial cell nests and broad strands between lymphoepithelial lesions (Fig 4).

From a clinical point of view, physicians must be aware of the indolent and generally localized nature of low-grade marginal zone B-cell lymphoma of the

TABLE 4. HISTOPATHOLOGIC FEATURES OF LOW-GRADE MARGINAL ZONE B-CELL LYMPHOMA OF MALT TYPE OF SALIVARY GLANDS

Dense lymphoid infiltrates diffusely involve gland or may form localized mass
Lymphoid cells express monotypic surface immunoglobulin
Plasma cells are also monoclonal
High-grade component is detectable
As with LESA/MESA, reactive lymphoid follicles and lymphoepithelial lesions usually are prominent
In contrast to LESA/MESA, centrocyte-like cells form broad "halos" around epithelial cell nests and broad strands between lymphoepithelial lesions

MALT type of the salivary glands. However, since MALT-type lymphomas have a significant risk of high-grade transformation,⁴ consideration should be given to treating these low-grade salivary gland lymphomas,¹⁴ even though they may not themselves behave in a progressive malignant fashion. Because few of the already-studied patients had a known adverse outcome, it is impossible to know which criteria are the best predictors of mortality, or when more aggressive therapies are indicated.

CONCLUSIONS

In conclusion, the diagnosis of LESA/MESA versus low-grade marginal zone B-cell lymphoma of the MALT type still relies on the evaluation of morphological features. It seems that molecular genetic analysis has little or no practical role in the clinical diagnosis of salivary gland lymphoma in a setting of LESA/MESA. Whether the different types of B-cell clonal expansion (oligoclonal versus monoclonal; localized versus disseminated) or genetic abnormalities¹⁸ may imply a different risk of lymphoma pro-

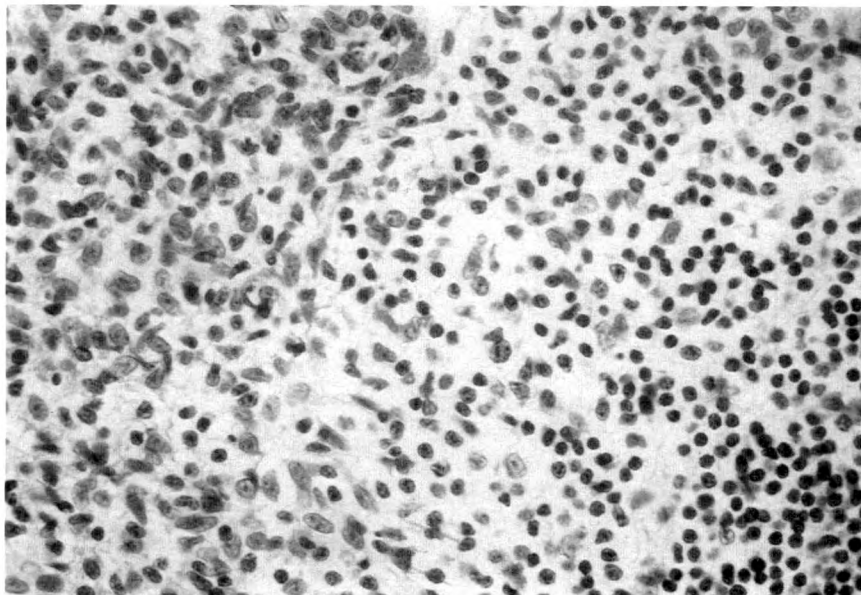


Fig 4. Low-grade marginal zone B-cell lymphoma of mucosal-associated lymphoid tissue type of salivary glands (H & E, original $\times 400$). Microphotograph shows broad strands of pale cells surrounding and extending away from lymphoepithelial islands, alternating with dark areas containing small lymphocytes.

TABLE 5. HISTOPATHOLOGIC AND CLINICAL CONTINUUM OF SALIVARY GLAND LYMPHOID PROLIFERATIONS

From benign-appearing and polyclonal

→ to MLDUS*

→ to low-grade lymphomas

→ to aggressive high-grade lymphomas

*Development of monoclonality appears to precede histologic evidence of neoplasia.

gression is under investigation.

In Table 5 is shown the pathological and clinical continuum of salivary gland lymphoid proliferations, that is, from benign-appearing and polyclonal to monoclonal lesions, to low-grade B-cell lymphomas, to aggressive high-grade B-cell lymphomas. Hopefully, further clinical and experimental studies should clarify the different steps of this biological and clinical progression.

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LETTERS TO THE EDITOR

To the Editor:

This letter is in regard to one of my articles, recently published in the *Annals of Otolaryngology, Rhinology & Laryngology* (Rebeiz EE, Wang Z, Annino DJ, McGilligan JA, Shapshay SM. Preliminary clinical results of window partial laryngectomy: a combined endoscopic and open technique. *Ann Otol Rhinol Laryngol* 2000;109:123-7). Dr Ollivier Laccourreye kindly pointed out to me that reference 3 is wrong, and I agree with him. I apologize for this error. The article in reference 3 (Laccourreye H, Lacau St Guily J, Brasnu D, Fabre A, Menard M. Supracricoid hemilaryngopharyngectomy. Analysis of 240 cases. *Ann Otol Rhinol Laryngol* 1987;96:217-21) was quoted by mistake and is not relevant to the discussion in the text. The following article should replace it: Laccourreye H, Laccourreye O, Weinstein G, Menard M, Brasnu D. Supracricoid laryngectomy with cricohyoidoepiglottomy: a partial laryngeal procedure for glottic carcinoma. *Ann Otol Rhinol Laryngol* 1990;99:421-6. This is the appropriate article and was the intended reference.

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To the Editor:

We read with interest the article by Ishiyama et al (Migraine and benign positional vertigo. *Ann Otol Rhinol Laryngol* 2000; 109:377-80), who found that migraine is more common in patients with idiopathic benign positional vertigo (BPV) than in patients with BPV secondary to trauma or surgery. With this communication, we would like to provide further evidence for the association of the two conditions.

For an ongoing study on migraine-associated vertigo, we assessed the lifetime prevalence of migraine in 200 consecutive patients from our dizziness clinic and 200 age- and sex-matched controls from an orthopedic ward. The diagnosis of migraine was based on a personal interview using the criteria of the International Headache Society. Among the 200 patients from our dizziness clinic, we identified 61 with BPV, 56 of whom had idiopathic BPV of the posterior semicircular canal. Stimulated by the report of Ishiyama et al, we compared these 56 BPV patients with 56 age- and sex-matched controls from the orthopedic group. The selection of this subgroup from the original 200 control subjects was based exclusively on the matching criteria of sex and age in 10-year intervals. The mean age was 60 ± 11 years (mean $\pm$ SD) in the BPV patients and 61 ± 12 years in the controls. We found a higher lifetime prevalence of migraine in the BPV group (32%) compared to the control group (16%; $p < .05$). Of the 18 patients with BPV and migraine, 11 had migraine without aura and 7 had migraine with aura. Fifteen patients were female and 3 were male — a finding that supports the view espoused by Ishiyama et al that the female preponderance in migraine may help explain why BPV occurs more frequently in women. In conclusion, there is little doubt that migraine and BPV are in fact interrelated. The question that remains to be answered concerns the pathophysiological link of these common disorders: is it genetic, ischemic, or something else?

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BOOK REVIEW

The Facial Nerve

Mark May and Barry M. Schaitkin, editors. Second edition. Hard cover, illustrated, indexed, 877 pages, 2000. Thieme, New York, NY, \$199.

Purpose: To provide a comprehensive clinical resource for physicians who are interested in managing patients with facial nerve disorders, that is, in terms of diagnosis, prognosis, and treatment, beginning with basic science and progressing to clinical evaluation.

Contents: The first of the book's 6 sections covers aspects of basic science and gives a review mainly of morphology and the experimental basis for nerve repair. The second section presents developments in diagnostic techniques and includes imaging studies. The third section focuses on management of patients with facial paralysis. Section 4 discusses the management of facial hyperkinesis. Section 5 provides a thorough account of the current status of surgery on the facial nerve. Section 6 is probably the best section of the book, in that it provides a thorough account of the rehabilitation techniques for facial paralysis, especially the surgical aspects. Other papers in this last portion of the book involve personal experiences with Bell's palsy on the part of the authors and others. There are 47 contributors. The first edition of this volume was published 10 years ago. This edition includes new developments and their clinical applications. Thirteen chapters from the first edition have been deleted, and their contents have been combined into other chapters. Eighteen of the 40 chapters are updated to include recent concepts.

Attributes and Limitations: This is an elephant-sized book on the subject of the facial nerve, made so by the numerous conditions or lesions that may involve the facial nerve. Much experience has been accumulated by the senior author from 3,500 patients with facial paralysis over a 35-year period. A sizeable portion of the book is dedicated to eye, nose, mouth, and reanimation techniques. (Here, especially, are burdening details welcome.) The least extensively discussed, though by no means the least important, is the so-called application for facial nerve decompression in the petrous portion of the nerve. The editors (at least Mark May) state that there is no evidence to support any decompression of the facial nerve for Bell's palsy. Therefore, notably absent is the "bottleneck" concept of Dr Ugo Fisch, which was one of the most innovative recent contributions to facial nerve surgery. Mentioning this contribution brings to mind the fact that so many names are attached to various aspects and features of the subject of the facial nerve. Besides that of Fisch, Adour's cranial polyneuritis theory comes to mind. An index of such names would have been helpful.

Applicability: This text has relevance to a wide spectrum of readers. Practicing physicians from varied specialties should find aspects useful in their clinical practice. Patients and their families can focus on specific topics such as physical therapy and techniques using hairstyle, facial cosmetics, eyeglasses, etc, to mitigate their problem. Surgery residents may find the combination of written format, patient examples, and medical drawings useful for review when facing new and challenging facial nerve problems. Medical students and other health care professionals who are consulted about an individual with facial paralysis may reference a chapter to gain perspective. In general, the text of this book is well written, although it may contain some repetition and esoteric subjects, especially in some of the tables. There is no doubt that one can benefit from its contents.

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SEVENTH SYMPOSIUM ON COCHLEAR IMPLANTS IN CHILDREN

Editors

BRUCE J. GANTZ, MD

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INTRODUCTION

The Seventh Symposium on Cochlear Implants in Children was held June 4-7, 1998, at the University of Iowa, Iowa City, Iowa. This conference was attended by more than 400 otolaryngologists, audiologists, speech-language pathologists, educators of the deaf, and others who are involved with hearing-impaired and profoundly deaf children. Participants included individuals from the United States and 17 foreign countries.

The 53 manuscripts included in this supplement are a peer-reviewed sample of the 61 presentations and 102 posters and exhibits. State-of-the-art presentations covered a broad range of topics, including new technologies and basic science, education and quality of life, language and educational issues, language and music, audiological evaluation of young children, candidacy and patient selection, expanding audiological criteria in children, implantation in children under the age of 18 months, perception, speech production, signal processing and electrode design, language, education, psychosocial issues, educational

placement of children with cochlear implants, social and economic impact of cochlear implants in Europe, surgery, and medical concerns.

Publication of this supplement has been made possible by generous grants from the Cochlear Corporation, Englewood, Colorado, and Advanced Bionics Corporation, Sylmar, California, and support of the National Institutes of Health/National Institute on Deafness and Other Communication Disorders (grant R13-DC08561-01).

We also express our sincere gratitude to all participants of the conference, those who gave excellent presentations on the podium and in poster sessions, and those who assisted with the review process. A special thanks to Dr Brian McCabe and the *Annals of Otology, Rhinology & Laryngology* for providing a venue for these manuscripts.

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ELECTRICALLY EVOKED COMPOUND ACTION POTENTIALS RECORDED FROM SUBJECTS WHO USE THE NUCLEUS CI24M DEVICE

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INTRODUCTION

In this paper, we describe some of our experience in recording the electrically evoked compound action potential (EAP) using the neural response telemetry system (NRT) of the Nucleus CI24M implant. The EAP is a direct measure of auditory nerve activity in response to an electrical stimulus, typically accomplished with an electrode in the cochlea or near the auditory nerve. The first work reported with cochlear implant users was accomplished by means of direct access to intracochlear electrodes for recording, either intraoperatively or in Ineraid cochlear implant users who have a percutaneous plug.¹⁻³ The NRT system in the Nucleus CI24M implant incorporates an internal amplifier and a reverse telemetry system that can sample the voltage on a specified electrode after stimulation. This system allows recordings to be made without externally placed electrodes or direct connections to internal electrodes. It is described more fully in a previous paper, along with a description of some limitations in this system and a protocol for measuring evoked potentials.⁴ The system has the ability to specify individual stimulating and recording electrodes in order to sample the neural response at different locations in the cochlea. Using the protocol described in that paper, we have been able, with appropriate stimulus and recording parameters, to successfully record potentials in 35 adults and 14 children.

Most of the examples presented in this report show data collected from adults, but each of the experiments that are described have also been conducted with children. In fact, it is important to stress that these recordings are particularly easy to make in children, in that they do not require the use of external recording electrodes. The subject can be awake, and some movement is acceptable, such as that which might occur while watching a video or reading or coloring a picture.

In this report we describe the EAP growth and refractory recovery measurements that have been our standard measurement tools in the past few years. The purpose of this paper is to describe several different methods by which to analyze the data collected with NRT. In addition, we present data collected with pulse train stimuli that may allow us to better characterize the response of the auditory nerve to stimuli with temporal patterns that are similar to the stimuli currently used with newer high-rate speech processors.

METHODS

Figure 1 illustrates the stimuli that are used to record the EAP. Two different techniques for measuring the re-

sponse are illustrated here. We refer to these 2 techniques as the “subtraction method” and the “direct method.” Generally, we find that using the subtraction method allows us to more effectively reduce artifact contamination. In many instances, however, we are able to record the EAP using a slightly more direct recording method. In this report, we compare results obtained from the standard subtraction method to a direct averaging technique in order to validate the subtraction method. Additionally, in some cases, use of the direct method allows us to record the response of the auditory nerve to more complex stimuli such as pulse trains.

The subtraction method takes advantage of the refractory properties of the auditory nerve to reduce stimulus artifact. As illustrated in Fig 1, four separate averages (A, B, C, and D) are obtained with interleaved stimuli. The probe-alone condition (trace A) has both stimulus artifact and response. The masker + probe condition (trace B), if the interpulse interval (IPI) is short enough to put the nerve into a refractory state at the time the probe is presented, consists of probe artifact only, with no neural response to the probe. By subtracting trace B from A, the stimulus artifact is eliminated, but the neural response remains. If the IPI is short, there can be neural response to the masker pulse in the interval following the probe. Consequently,

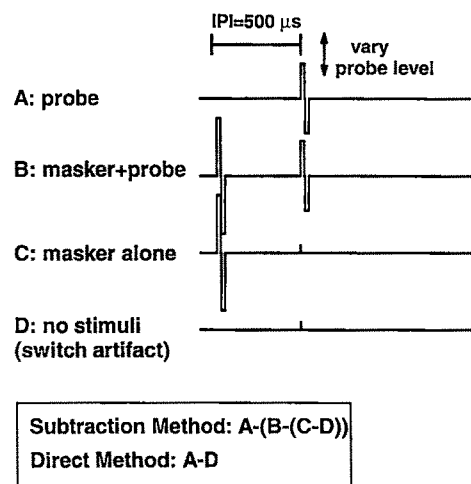
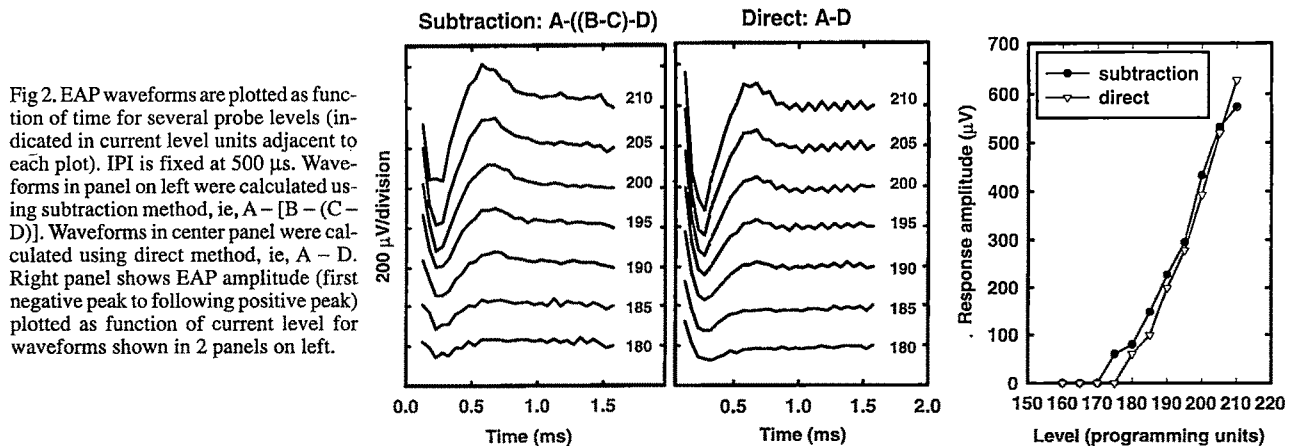


Fig 1. Schematic of stimuli used in neural response telemetry system (NRT) measurements to obtain electrically evoked compound action potential (EAP) growth function. Using subtraction method, ie, $A - [B - (C - D)]$, growth function is obtained by fixing masker level at level near top of subject's dynamic range. Interpulse interval (IPI) is fixed at 500 μ s in order to ensure that nerve is refractory in masker + probe condition. Level of probe is then varied across dynamic range. Using direct method, ie, $A - D$, we have used same data, but only traces A (probe alone) and D are used to calculate response.



we perform another subtraction of the response recorded in the masker-alone (trace C) condition. Finally, as noted in the schematic by a vertical line, there is a relatively small switching artifact that is inherent in the recording system at the time of the probe pulse in trace C. That switching artifact is minimized by performing 1 final subtraction of the no-stimulus condition (trace D).

As illustrated in Fig 1, to measure an EAP response using the direct recording method, we simply subtract the response recorded in the no-stimulus condition (trace D) from the response recorded in the probe-alone condition (trace A). In many cases, the probe stimulus artifact is small enough that we are able to resolve the response without use of the subtraction technique outlined above. The direct measures provide a simpler method of recording responses in some subjects (using fewer stimulus presentations), which results in a better signal-to-noise ratio. In addition, this method provides a way to assess responses to more complex stimuli, such as pulse trains, as noted below.

To measure an EAP growth function using the subtraction method, we fix the IPI at 500 microseconds and fix the level of the masker pulse to a high current level. Then

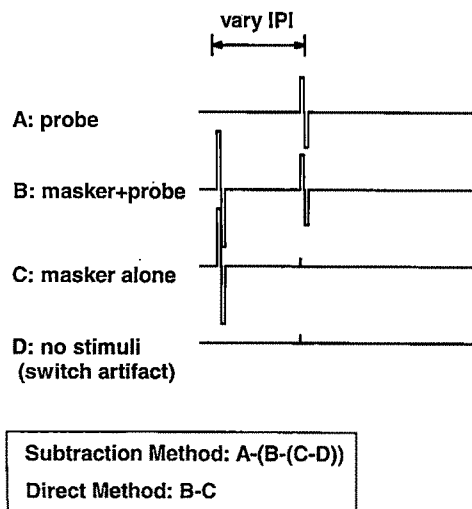


Fig 3. Schematic of stimuli used in NRT measurements to obtain EAP recovery function. Subtraction method is $A - [B - (C - D)]$. Direct method is $B - C$.

the level of the probe is systematically varied. In instances in which the stimulus artifact is particularly small, we are also able to record an EAP growth function using the direct recording technique. In those cases, we simply vary the level of the probe to acquire a growth function.

Variations on these basic recording techniques are used to record EAP refractory recovery functions and to record the response of the auditory nerve to pulse train stimuli. These variations are described below.

RESULTS AND DISCUSSION

Examples of responses measured with both techniques are illustrated in Fig 2. Waveforms recorded for different probe levels are shown. The waveforms are similar in both the subtraction and direct recording techniques. The graph at the right shows EAP growth functions as the amplitude of the responses (measured from the first negative peak to the following positive peak), plotted as a function of stimulus level, for responses recorded by both the subtraction and the direct recording methods.

We wish to stress several points relative to these data. First, these direct recordings do not use alternating-polarity stimulation; ie, there is no procedure used here to eliminate stimulus artifact. Nevertheless, the residual stimulus artifact apparent in the response interval is minimal. Second, the quality of response separation from the artifact obtained by the direct method demonstrated in this example is not possible in all subjects. We have greater success using the subtraction method. Finally, we can view these results as a validation of the methods implemented in the NRT software. The rather complex series of subtractions yields results identical to direct recordings in this example. Viewed in the opposite way, the apparent response recorded with the direct method demonstrates refractory properties that would be expected of a neural response as recorded by the subtraction method.

Figure 3 illustrates the stimuli used for measuring EAP refractory recovery functions. In order to assess the rate at which the auditory nerve recovers from refractoriness, we presented 2 stimuli separated by a short IPI. These stimuli are essentially the same stimuli shown in Fig 1, but in this case we fix the level of the masker and probe and then vary the IPI. The subtraction method is the same as the one in the previous schematic. The direct method

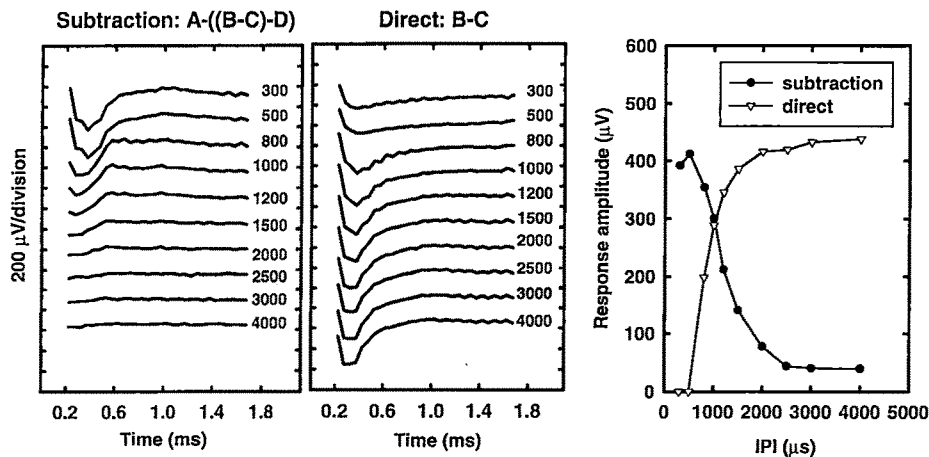


Fig 4. EAP waveforms are plotted as function of time for several values of IPI (indicated in microseconds adjacent to each plot). Stimulus levels for both masker and probe were set in upper part of subject's dynamic range. Waveforms in left panel were calculated using subtraction method, ie, $A - [B - (C - D)]$. Waveforms in center panel were calculated using direct method, ie, $B - C$. In panel on right, amplitude of response (first negative peak to following positive peak) is plotted as function of IPI for waveforms shown in 2 left panels.

assesses the response to the probe with the masker present (trace B), but the residual response to the masker pulse must then be subtracted ($B - C$).

Figure 4 illustrates a series of EAP waveforms recorded from the same subject by the 2 methods. With the direct method, at short IPIs the response to the probe is small, as a result of refractory effects. As the IPI is increased, there is greater response to the probe in the masker + probe condition. With the subtraction method, the difference between the probe-alone and masker + probe conditions is large for short IPIs, but the amplitude decreases with increasing IPI. The resulting recovery functions are therefore opposite one another, as shown in the amplitude-versus-IPI plot at the right, but they show a similar time course of recovery, suggesting that they tap into the same temporal properties of the neural recovery process.

The responses to continuous stimulation through a cochlear implant may be characterized to some extent by refractory properties as measured with 2-pulse stimuli as in Fig 4. The extent to which other factors, such as cumulative adaptation and stochastic nerve discharge, may have

an effect on the responses can be evaluated in a more comprehensive way by using trains of pulses. The NRT software does not allow for direct averaging of the response to each pulse in a train. By using a modification of a technique used by Wilson et al,⁵ illustrated in Fig 5, we have been able to evaluate responses to individual pulses in a train. To measure the response to the n th pulse in a train, we set the number of masker pulses to $n - 1$. Trace B is then a series of n pulses, and trace C is a series of $n - 1$ pulses. The response $B - C$ is therefore the response to the last pulse in the train. To measure the response to the first 15 pulses of the train, n is varied and 15 different averaged responses must be collected.

An example of responses to pulse train stimuli measured with NRT is shown in Fig 6. The waveforms measured in response to each pulse are arranged according to pulse number. A clear alternating pattern of response is observed in response to the constant-level pulse train. We interpret this alternating pattern to be at least partially the result of refractory recovery properties, eg, many fibers being refractory in response to the second pulse but recovered at the time the third pulse is presented.

Each of the measures illustrated in these graphs — growth functions, refractory recovery functions, and the

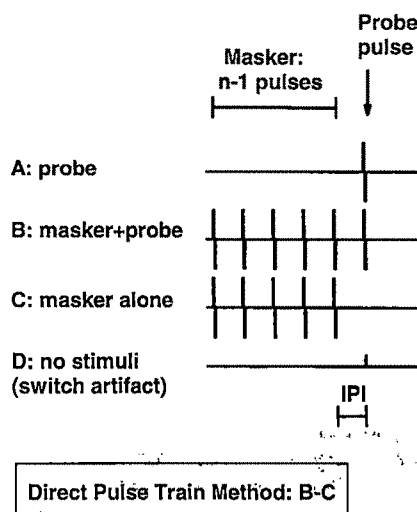


Fig 5. Schematic of stimuli used in NRT measurements to obtain responses to pulse trains. Levels of probe and masker pulses are fixed. IPI is set to inverse of masker pulse rate so that if number of masker pulses is $n - 1$, masker + probe stimulus is uniform series of n pulses.

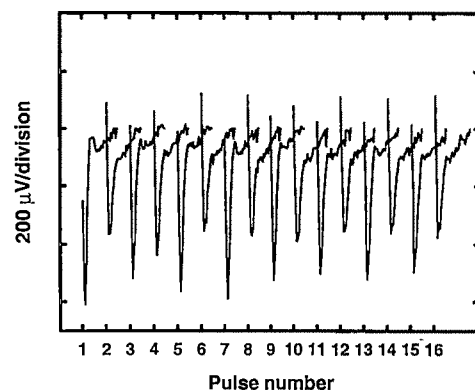


Fig 6. This graph is series of waveforms showing response to series of pulses with fixed amplitude presented at a rate of 1,000 pulses per second. Responses are calculated using method illustrated in Fig 5 and described in text. Response to each successive pulse in train is shown as function of pulse number. Responses show alternation in amplitude of response that is typical of these data.

response to pulse trains — can vary across subjects and across stimulating electrodes within a subject.^{2,5,6} The degree to which these variations among subjects and electrodes may be related to the perception of electrical stimulation is an important issue in applying such measures in a clinical population. Other studies will assess the degree to which these particular electrophysiological measures compare to specific psychophysical tests, as well as to measures of speech perception.

SUMMARY

The ability to directly measure the response to a pulse with the NRT opens the possibility of using this system to characterize the responses to more complex stimuli. An example is the responses to constant-amplitude pulse trains. With further changes in the software that controls the implant, it may be possible to characterize the responses to modulated pulse trains or other stimuli that better approximate the type of stimuli that are normally

used with a cochlear implant speech processor.

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INITIAL RESULTS OF NEURAL RESPONSE TELEMETRY RECORDING OF ELECTRICAL COMPOUND ACTION POTENTIALS FROM THE UNITED KINGDOM

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INTRODUCTION

The data presented here are from a larger study undertaken to characterize the growth and recovery functions of the electrical compound action potential (ECAP) response across a large group of adult cochlear implant users in a multicenter trial. More than 60 adults across 11 European cochlear implant centers participated in this stage 2 trial. All centers carried out measurements on a minimum of 3 to 5 electrode pairs spaced in the basal, central, and apical areas of the electrode array. Testing was completed as part of an outpatient session, with Windows-based software (NRT v2.0) developed by Dr N. Dillier and others at the University Hospital, Zurich, Switzerland. All participants followed a strict protocol to ensure comparability of results across centers.

Neural response telemetry (NRT) is a technique for recording the ECAP that has rapidly evolved from a research method developed by Brown and Abbas.¹ The original development was accomplished with patients using the Ineraid device, in which direct access to individual electrode pairs was available. The technique involves recording the neural response to a series of 3 different stimulation conditions: 1) probe presented alone; 2) probe presented with a masker pulse, the two being separated in time by a short masker advance, so that the nerve is in refraction and unable to respond to the probe stimulus; and 3) masker presented alone. A subtraction algorithm, ie, $A - (B - C)$, extracts the true neural response to the

probe stimulus from the stimulus artifact. The technique has now been implemented in the Nucleus CI24M device by using telemetry to transmit information on the recorded response from the implanted component back to the programming system.

Neural response telemetry has potential value in programming patient's implant maps, particularly in young children, in whom accurate subjective threshold and comfort levels to electrical stimulation are difficult to obtain. Therefore, the goal of NRT research is to assess the characteristics of ECAPs recorded with NRT, to help with optimizing individuals' map parameters. This stage of research was largely meant to characterize the growth and recovery functions obtained in a wide range of adult users.

CLASSIFICATION SYSTEM FOR ELECTRICAL COMPOUND ACTION POTENTIAL RESPONSE MORPHOLOGY OBTAINED BY NEURAL RESPONSE TELEMETRY

Class	Description	Proportion (%)
A	Good response, N1 and P1 clearly visible	45
B	Good response with double positive peak	0
C	Clear response, P1 but no clear N1	39
D	Clear response, N1 but no P1	2
E	Visible response but poor quality (jagged)	0
F	Bad or no response, noisy or artifactual	14
Proportion is calculated as percentage of stimulated electrode sites tested, n = 56.		

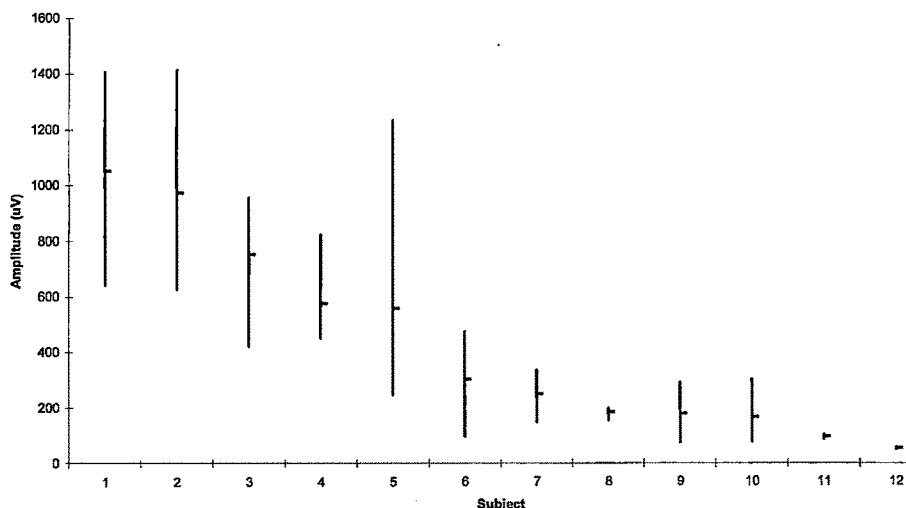


Fig 1. Amplitude of electrical compound action potential (ECAP) responses. For each subject, maximum ECAP amplitude (A_{max}) was measured for each stimulated electrode site. Bar shows range of A_{max} ; average A_{max} is shown with horizontal line. There is clearly wide range of maximum amplitudes obtained across subjects from 5 stimulated electrode sites.

METHODS

The patients were tested as part of a routine outpatient visit, at least 1 month after initial tuning, and provided a stable map was established. By the normal ascending technique, subjective thresholds (T levels) and maximum acceptable loudness levels were obtained (at the mapped pulse width) at 250-, 1,000-, and 80-Hz stimulation rates. The normal WinDPS software was used for this process. These rates were chosen as 1) the rate used in normal programming, 2) a faster rate that may be used in the fu-

ture, and 3) the rate used for recording the ECAP with the NRT software. In earlier stages of NRT research, normal comfort (C) levels from the patient's map were sometimes inadequate for recording reliable ECAP responses. At the slower stimulus rate of 80 Hz, the stimulus was found to be subjectively quieter, so most patients were able to tolerate a stimulus level higher than the C level. For clear ECAP responses to be recorded, a loudest acceptable presentation level (LAPL) was therefore used as a starting point. This was measured with the "stimulate-only" facil-

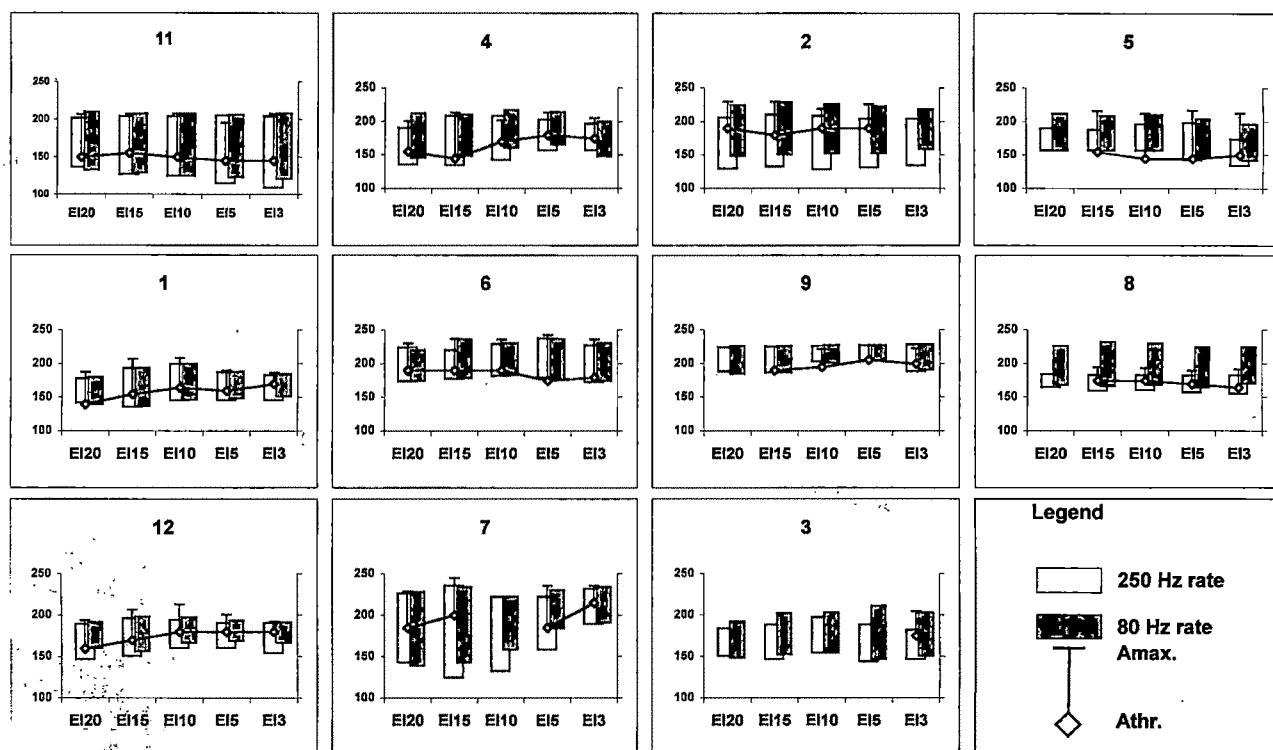


Fig 2. Subjective and neural response telemetry (NRT) thresholds and ranges by subject and by stimulated electrode (EI). Each panel shows results from 1 of 11 subjects for whom protocol was completed. Y axis is in stimulus current units, category axis indicates stimulated electrode, and subject number is indicated at top center of each panel. Subjective range is indicated by floating bars; open bars indicate range from subjective threshold to loudest acceptable presentation level (LAPL) at 250-Hz stimulation rate. Shaded bars show similar data for 80-Hz stimulation rate (NRT rate). Open diamond indicates stimulus current level for calculated ECAP threshold (A_{thr}). This is linked to horizontal bar indicating stimulus level at which maximum ECAP amplitude (A_{max}) was reached. Looking across different subjects, it is clear that A_{thr} is not consistently related to subjective threshold or LAPL. However, within subjects, A_{thr} seems to fall at fairly consistent point in subjective range. See text for further discussion.

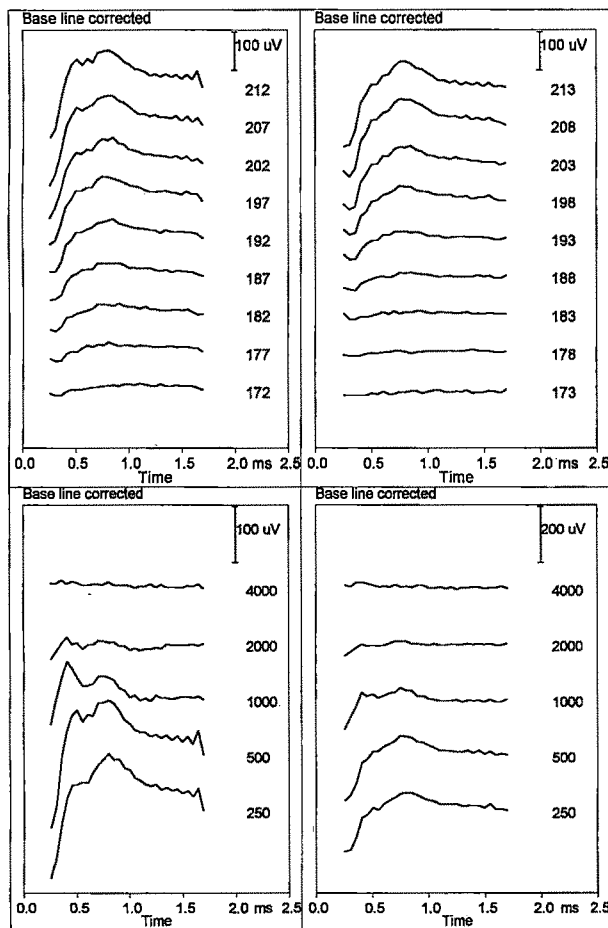


Fig 3. Sample ECAP series from subject 12. Upper panels show amplitude growth series; numbers to right of traces indicate stimulus current units. Lower panels show recovery series; numbers to right of traces indicate masker advance in microseconds. Left panels are from stimulation electrode 15, which was classified as type C; right panels are from electrode 10, classified as type A.

ity within the NRT software. Recordings used a monopolar arrangement for both stimulus and recording electrode pairs, eg, stimulating between electrode 3 and MP1 and recording between 5 and MP2.

For ECAP responses to be recorded, there was an initial phase of making trial recordings at various stimulation parameter settings to optimize trace quality. After parameter optimization, 2 sets of recordings were obtained: a recovery series and an amplitude growth series. For the recovery series, recordings were made for at least 5 masker advance settings between 250 and 4,000 μ s. Masker advance is the time between delivery of the masker and probe pulses, also known as the interpulse interval (IPI). For the amplitude growth series, recordings were made from LAPL down to the T level at a fixed masker advance of 500 μ s. Each of 5 electrodes was tested separately; once we were familiar with the recording process, a full set of measurements on 5 electrodes could be obtained in about an hour. Results were stored to a disk from the NRT program in a text file format; this allows results to be analyzed off-line either in the NRT program or on an external program such as Microsoft Excel.

RESULTS

Twelve patients were assessed between the 2 centers in the United Kingdom; 11 of these patients completed the protocol. Only the amplitude growth results are discussed here. The initial evaluation was carried out with NRT v2.0 software to assess the presence and type of responses obtained. The Table describes a classification system that was devised to categorize response types by morphology, along with the proportion of each type found. With this classification, the results showed no obvious pattern in relation to patient or electrode. In total, 56 electrode sites were tested; 86% produced a recognizable response (types A to D), demonstrating that successful recordings can be obtained for most electrode sites tested.

Figure 1 shows the maximum amplitude of responses, ordered by the average of the maximum response amplitude across electrodes, within patients. The amplitude was measured between N1 and P1 peaks when both were present; when no N1 peak was present, the most negative point of the waveform was used. It is acknowledged that this will underestimate amplitude when no N1 peak is available.

Figure 2 plots each patient's T level and LAPL, along with the ECAP threshold and level at maximum ECAP amplitude, for each electrode. The ECAP threshold was calculated by a linear extrapolation from the amplitude growth function, and the point of intersection of this extrapolated line with the zero voltage axis was taken as the threshold. This method resulted in an apparent ECAP (NRT) threshold below subjective T levels in some cases. This is most likely due to some series' being stopped before the ECAP response had disappeared, thus distorting the linear extrapolation calculation. It is possible that some subjects have a "true" objective threshold below their subjective threshold at this low rate of stimulation. Alternatively, there may be differences in the characteristics of the stimuli delivered by the WinDPS compared with NRT software.

Figure 3 illustrates a typical type A and type C response series from 1 subject (subject 12).

DISCUSSION AND CONCLUSIONS

The ECAPs were successfully recorded in the majority of patients and electrodes tested with NRT v2.0. A simple classification system demonstrates that around half of these successful recordings are clear, with both N1 and P1 peaks visible. However, a significant number do not demonstrate a clear N1 peak, so that measurements of amplitude are prone to underestimation. However, where an N1 peak is not seen at higher stimulus levels, it is often revealed at lower levels (eg, Fig 3, upper left panel), allowing a better resolution of amplitude growth function at threshold. There is a wide range of response amplitudes, but no significant correlation of maximum response amplitude with age or gender. Although the numbers are too small here for formal analysis, a possible correlation seems apparent between maximum amplitude and speech performance.

Between subjects, there is wide variation in the levels of NRT threshold compared to subjective measures, at both of the lower stimulation rates. At this stage, this implies a weak relationship between NRT and subjective T or C levels, which would not significantly aid the setting of map parameters. Further analysis of group data is needed before any firmer conclusions can be drawn. However, within subjects there appears to be a reasonably consistent relationship across electrodes; and this may prove useful when extrapolation of thresholds is needed.

Recovery functions are potentially of particular use in deciding on a processing strategy using faster rates of stimulation. At this stage, no detailed analysis of recovery functions has been undertaken. However, it is notable that maximum amplitude is often seen at a masker advance of 500 μ s, rather than the shortest setting used of 250 μ s. Theory would suggest that the auditory nerve is in full refraction at both of these settings. This finding may be artifactual, because type C responses are often seen, and the amplitude may be underestimated. However, there may be some

other measurement-related artifact present that needs further investigation. At such brief intervals between the masker and probe pulses, it is also possible that there are components of the response to the masker pulse within the combined masker-probe stimulus occurring after the time that the probe is delivered. Subtraction of this component would tend to distort (and probably reduce) the amplitude of the extracted response. This suggests an inherent weakness in the use of this subtraction algorithm for ECAP recordings of recovery functions when short (<500 μ s) masker advances are employed.

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BRAIN ACTIVITIES OF PRELINGUALLY AND POSTLINGUALLY DEAFENED CHILDREN USING COCHLEAR IMPLANTS

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INTRODUCTION

The speech perception performance of prelingually deafened cochlear implant (CI) users who receive CIs during the speech acquisition period is generally better than that of patients who undergo cochlear implantation after this period. To evaluate the differences in brain activities between prelingually and postlingually deafened children using CIs, we measured the regional cerebral blood flow (rCBF) during silence and speech activation in 3 children who underwent cochlear implantation.

MATERIALS AND METHODS

We examined 3 CI users, 1 of whom was deafened postlingually (patient 1) and 2 of whom were deafened prelingually (patients 2 and 3), using positron emission tomography (PET). The patients underwent cochlear implantation at 8 to 10 years of age. We measured the rCBF twice in the prelingually deafened subjects. We also measured the rCBF in 4 prelingually and 6 postlingually deafened adults with CIs as controls. All subjects were right-handed. The CI they used was a 22-channel system (Cochlear Ltd, Melbourne, Australia).¹ The lengths of CI use in the prelingually deafened patients were 2 and 4 years at the first PET scan and 5 and 7 years at the second scan, respectively, while that in the postlingually deafened patient was 1 month.

Informed written consent was obtained for all patients

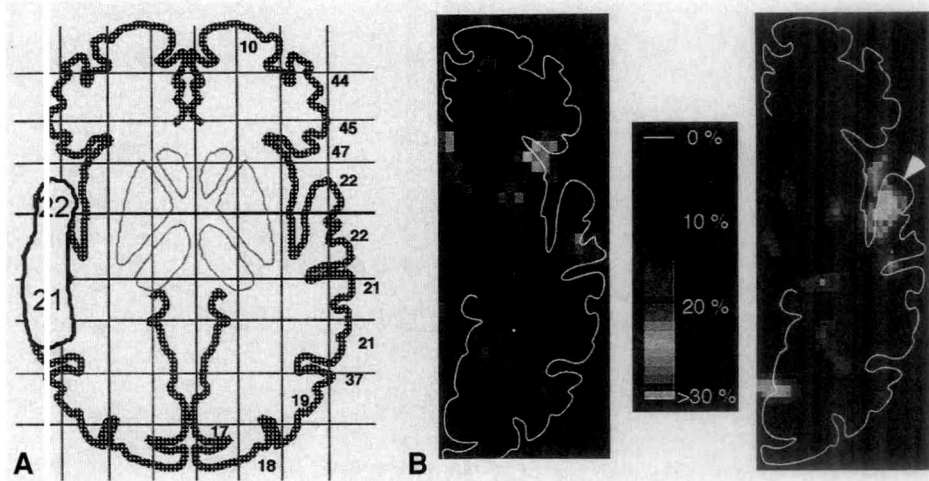
after a full explanation of the study. This study was approved by the Ethics Committee of the Kyoto University Faculty of Medicine.

For evaluation of speech perception performance, we presented 5 Japanese vowels (/u/, /o/, /a/, /e/, /i/) without lipreading in a vowel recognition test. In a consonant recognition test, we used 13 Japanese consonants in consonant-vowel syllables (/pa/, /ta/, /ka/, /ba/, /da/, /ga/, /ha/, /sa/, /za/, /ma/, /na/, /ra/, /ja/) without lipreading. We calculated the percentages of correct answers.

For the rCBF measurement, we measured the rCBF in 2 different conditions — no sound stimulation and speech sound stimulation — through a CI by PET using ¹⁵O-labeled water. The head was scanned for radioactivity with a multislice PET scanner (PCT 3500W, Hitachi Medical Co, Tokyo, Japan) for 120 seconds from the beginning of the H₂¹⁵O injection. All data were linearly scaled to adjust the intercommissural distance of each subject to that of Talairach and Tournoux's standard brain atlas,² and the scaling factor was applied in all directions. Details of the methods used for rCBF measurement are described in a previous report.³

To search for changes in rCBF for auditory processing, we established a region of interest (ROI) on the midportion of the superior and the middle temporal gyri (auditory association area, Brodmann's areas 22 and 21; see Figure,

Setting of ROI and corresponding speech-activated PET images in patient 2. A) Region of interest for regional cerebral blood flow (rCBF) measurement; midportion of superior and middle temporal gyri (auditory association area; Brodmann's areas 22 and 21). B) Horizontal section that includes auditory association area of prelingually deafened child (patient 2). In first positron emission tomography (PET) scan (left image), rCBF increase was limited. In follow-up PET image after use of cochlear implant for 3 years (right image), rCBF increase in left auditory association area (arrowhead) became larger with improvement of speech perception.



A). The PET data from the silent condition were subtracted from those from speech stimulation to determine changes in rCBF. The percent changes of rCBF in the ROI were measured for speech stimulation.

RESULTS

The vowel recognition performance in the postlingually deafened child was 76%, and the consonant recognition performance was 44%. In the 2 prelingually deafened children, the vowel recognition performances were 88% and 32%, and the consonant recognition performances were 3% and not available, respectively, at the first PET scan. At the second PET scan, the speech perception performance of 1 prelingually deafened patient (patient 2) had improved from 3% to 23% in consonant recognition, whereas that of the other (patient 3) was unchanged.

The Figure shows speech-activated PET images of a prelingually deafened child (patient 2) with improvement of consonant perception as he continued to use a CI. At the first PET scan, the increase in rCBF in the left auditory association area was limited. In the follow-up PET image made after use of a CI for 3 years, the increase in rCBF in the left auditory association area was larger, correlating with an improvement in speech perception.

When speech stimuli were given to the subjects, the rCBF increase in the postlingually deafened child (patient 1) was significantly larger than those in the prelingually deafened children (patients 2 and 3; Table 1). In the follow-up studies, the rCBF increase in the left audi-

tory association area in patient 2 was larger than that in the first PET study, while that in patient 3 was unchanged. In adult CI users, the mean rCBF increase in the auditory association area in prelingually deafened subjects was smaller than that in postlingually deafened subjects.

With no sound stimulation, the rCBF values in the auditory association area in the prelingually deafened children (patients 2 and 3) were similar to those in the prelingually deafened adults (Table 2). These values are higher than those in the postlingually deafened adults. In the follow-up studies, the rCBF in the silent condition was decreased as the children continued to use the CIs. In the postlingually deafened child (patient 1), the rCBF in the auditory association area was slightly lower than those in the prelingually deafened children but higher than those in the postlingually deafened adults.

DISCUSSION

In the prelingually deafened children we examined, speech activation in the auditory association areas was very limited. This finding was basically identical to that for prelingually deafened adults. In the postlingually deafened child we examined, the speech-induced rCBF increases in auditory association areas were larger than those in the prelingually deafened children and were compatible with those of postlingually deafened adults. These findings suggest that the plasticity or ability to reorganize of the auditory association areas is limited in individuals 8 years of age or older. However, in the present

TABLE 1. SPEECH-INDUCED INCREASE IN REGIONAL CEREBRAL BLOOD FLOW IN AUDITORY ASSOCIATION AREA

		Increase (%)	
		Right	Left
Patient 1		10.2	12.5
Patient 2	First scan	5.1	6.7
	Follow-up	2.0	12.2
Patient 3	First scan	2.7	-5.1
	Follow-up	2.7	-2.0
Prelingually deafened adults (n = 4)		2.9	6.3
Postlingually deafened adults (n = 6)		13.7	12.5

TABLE 2. REGIONAL CEREBRAL BLOOD FLOW IN AUDITORY ASSOCIATION AREA WITH NO SOUND STIMULATION

		Flow (mL/s per 100 g brain)	
		Right	Left
Patient 1		64.3	70.3
Patient 2	First scan	74.9	73.4
	Follow-up	67.2	68.9
Patient 3	First scan	76.8	77.7
	Follow-up	61.6	61.8
Prelingually deafened adults (n = 4)		73.0	70.7
Postlingually deafened adults (n = 6)		63.7	59.5

study, 1 prelingually deafened CI user (patient 2) exhibited a remarkable rCBF increase in speech activation in the left auditory association area after 3 years of CI use. This finding suggests that the auditory cortices of children age 8 years or older may still have some plasticity and that more neuronal networks become available to process auditory signals coded by the CI as patients continue to use it.

With no sound stimulation, both prelingually deafened children and adults exhibited higher rCBFs in the auditory association areas than did the postlingually deafened adults. These activities in the auditory association areas during rest were considered unrelated to sound signal processing. Veraart et al⁴ reported that glucose utilization in the visual cortex of human subjects who became blind early in life was increased, but that of subjects who became blind after completion of visual development was decreased. This difference between early- and late-blinded subjects is compatible with our findings. The high activities in early-deafened auditory cortices may reflect the persistence of supernumerary synapses that would escape the normal developmental decrease in synaptic density during infancy.

In the prelingually deafened child whose rCBF increase in the auditory association area did not change between the 2 measurements (patient 3), the rCBF during silence was decreased. This finding suggests that the auditory as-

sociation areas are involved in language processing of lip-reading; this patient had made progress in lipreading as he continued to use a CI.

In the postlingually deafened child we examined, the rCBF in the auditory association area was slightly lower than those in the prelingually deafened children we examined, but higher than those in postlingually deafened adults. This patient lost his right-ear hearing from meningitis at 4 years of age and became bilaterally deaf at 9 years of age as a result of a traffic accident. Unilateral deafness during the speech acquisition period may affect the neuronal networks in the auditory association areas such that some neurons become active even without sound stimulation.

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RELIABILITY OF THE NUCLEUS CI22 AND CI24M COCHLEAR IMPLANTS

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INTRODUCTION

The reliability of cochlear implants is becoming an increasingly important factor for patients and clinicians when deciding on implantation. With more than 18,000 individuals worldwide having received Nucleus cochlear

implant systems over the last 15 years, Cochlear Pty Limited, Lane Cove, Australia (Cochlear) has accumulated a significant experience in implant technology. Cochlear is the only manufacturer that has been routinely publishing data on long-term reliability.¹⁻³ This paper describes mea-

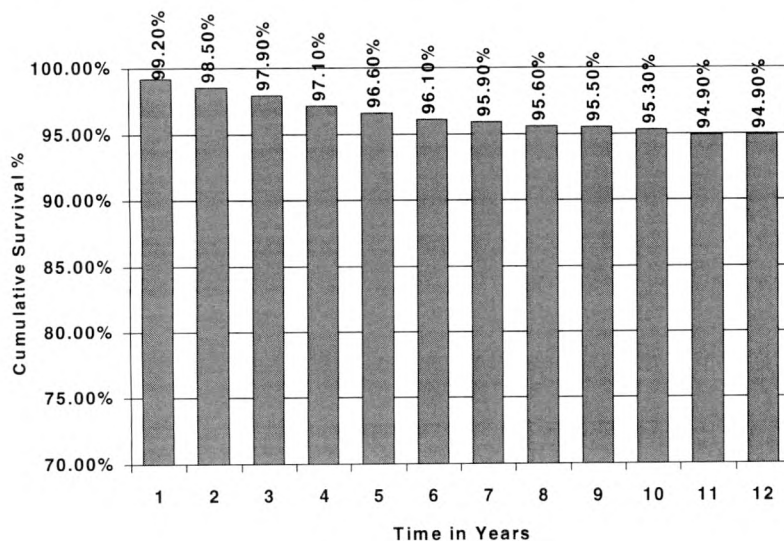
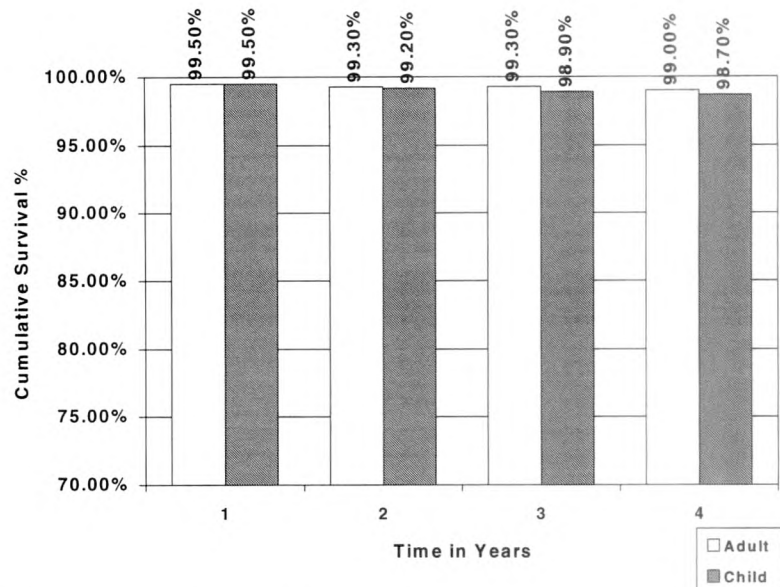


Fig 1. Cumulative survival on 70% to 100% scale for all patients implanted with Nucleus CI22 Cochlear Implant (N = 16,427). Data are as of December 31, 1997.

Fig 2. Cumulative survival on 70% to 100% scale for adults and children implanted with Nucleus CI22 Cochlear Implant (N = 8,145) after introduction of design changes implemented in 1993. Each column represents at least 200 users. Data are as of December 31, 1997.



asures of reliability and presents updated data for the Nucleus 22 and the Nucleus 24 cochlear implant systems as of December 1997.

METHODS

The reliability was measured from the cumulative experience report, a standard method applied by medical device manufacturers to assess highly reliable devices such as pacemakers or cochlear implants.⁴ This method describes the device history and provides an evaluation of the number of failures that have occurred as a function of how long the device has been in use. The percentage of devices surviving until a certain device age is expressed as cumulative survival.

The cumulative survival percentage is calculated for specific time intervals — for example, 1-year intervals — and takes into account 3 measures. These measures are the number of devices that were in use by recipients and were functioning normally during that time period; the

number of hard failures that required explantation because they did not perform according to specification; and the number of devices that were removed for other (eg, medical) reasons. The percentage of devices surviving in each time period is then calculated. Cochlear's definition of hard failures includes devices requiring explantation as a result of design weakness, manufacturing faults, or external impact to the head. This failure definition also includes cases in which loss of clinical benefit resulted in explantation necessitated by an excessive number of electrode faults or due to intermittent operation.

The calculation of the cumulative survival percentage is in contrast to the common practice of calculating the failure percentage whereby the number of failures is divided by the number of devices in the field. The failure percentage has the major limitation that the length of device use is not taken into account. The cumulative survival percentage gives a factual representation of the reliability of a device over time without making statistical assumptions and therefore allows comparison of device reliability at different durations of implant usage.

RESULTS

Taking all implanted Nucleus CI22 implants into account (N = 16,427), the cumulative survival percentage at 12 years of implant use is 94.9% (Fig 1). The major causes for failure included damage to the receiver antenna or the electrode array exit due to external stress and damage to internal components due to electrostatic discharge. As part of an ongoing quality improvement program, Cochlear has introduced several design modifications over the years that have increased the reliability of the device to a cumulative survival percentage of 99.0% for adults and 98.7% for children at 4 years of implant life (Fig 2). The average of this data (98.8%) compares favorably with the cumulative survival of 97.1% at 4 years found before the introduction of the modifications (Fig 1). The CI22 titanium implant package encapsulated in silicone elastomer has proven extremely reliable.

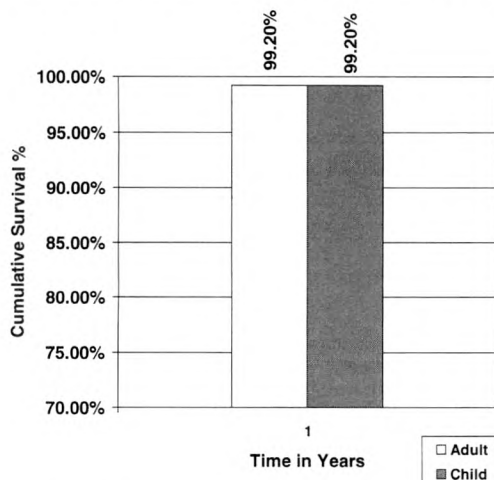


Fig 3. Cumulative survival on 70% to 100% scale for adults and children implanted with Nucleus CI24M cochlear implant (N = 1,650). Data are as of December 31, 1997.

The design of the new Nucleus CI24M cochlear implant has taken advantage of the learning experience obtained with the CI22 implant. Experience with more than 1,650 CI24M devices implanted shows that the cumulative survival at 1 year of implant use is 99.2% for adults and children (Fig 3). As part of the ongoing quality program, Cochlear has implemented a design change to improve the CI24M implant further. Reliability data on the modified device will be reported once sufficient field experience has been collected.

CONCLUSION

The cumulative experience report for all implanted CI22 and CI24M cochlear implants shows that both devices

are very reliable. Reliability is and will be one of the important criteria in the selection of cochlear implants.

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NEW CLARION ELECTRODE WITH POSITIONER: INSERTION STUDIES

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A new straight thin electrode array (universal electrode) was designed to be used together with a positioner, which will place the electrode array at the medial wall (modiolus) of the cochlea. The study objectives were to demonstrate safety and ease of insertion, tissue trauma, electrode position, and depth for universal and standard electrodes in human temporal bones; to test functional properties in cats; and to determine the surgical procedure and electrophysiological benefits in a clinical study. The cadaver study demonstrated the ease of insertion for the universal electrode and the positioner without tissue damage. An average gain of insertion depth of 180° was achieved with the positioner. Animal studies demonstrated a reduction in threshold of 6 dB for the electrical auditory brain stem response (EABR). Neither additional cochlear damage nor additional connective tissue formation was found. The intraoperative human study findings showed a marked reduction of threshold for both EABR and stapedius reflex thresholds. Impedances were increased. Plain x-rays demonstrated modiolus proximity of the electrode with the positioner. The new Clarion electrode with positioner is a relatively safe design for providing modiolus proximity. The electrophysiological benefits include reduction of threshold and power consumption.

INTRODUCTION

Most cochlear implants use straight electrode arrays that are positioned on the lateral wall of the cochlea.^{1,2} The preformed standard Clarion 1.2 electrode provides a modiolus-hugging position, but not in all patients. This position, however, has potential benefits. The proximity to the ganglion cells will reduce the thresholds for excitation and, in all probability, enlarge the dynamic range, improve channel separation, and reduce power consumption.^{3,4}

Several attempts have been made to design modiolus-hugging electrodes without potential damage to cochlear structures.⁵ However, no concept has proved fully convincing. This new electrode design with a protective positioner was subjected to the following studies in order to demonstrate safety and effectiveness.

ELECTRODE DESIGN

A new straight thin electrode was developed with an increased contact surface. The 16 contacts on the 20-mm array are all oriented toward the medial side of the cochlea. The mechanical properties provide high directional preponderance with a slight curve toward the modiolus. The electrode can be used without or with the protective positioner (Fig 1). The electrode can be inserted with the standard Clarion insertion tool. The protective positioner is a

concave, prebent silicone carrier that covers the electrode on the lateral side. When inserted after electrode insertion, it will place the electrode carrier at the medial wall of the cochlea. The positioner can also be used with the standard Clarion electrode (Fig 2). The positioner is provided together with a modified insertion tool with a stylet to straighten the positioner (Fig 3).

STUDY OBJECTIVE

This new universal electrode had to be evaluated with-

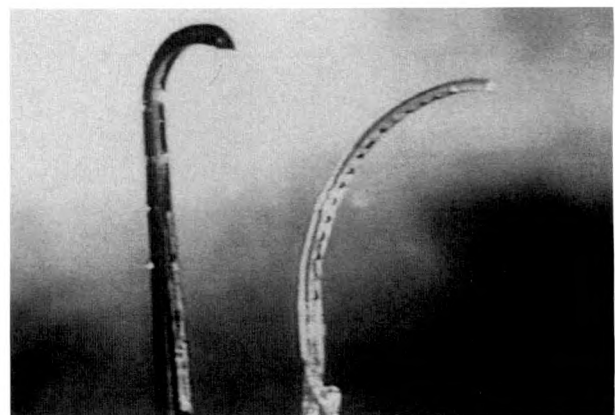


Fig 1. New universal electrode with protective positioner.

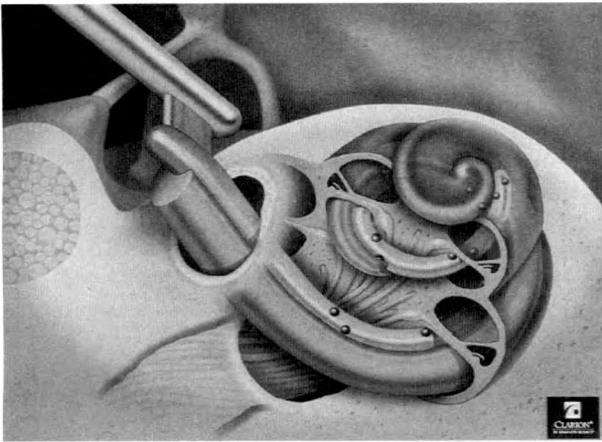


Fig 2. Schematic view of standard Clarion electrode in scala tympani with positioner.

out and with a positioner, to include assessment of the following factors: ease of insertion in cochleostomy, flexibility of electrode and positioner, insertion trauma or tissue damage, electrode and positioner insertion depth, proximity to the modiolus, and insertion effectiveness.

MATERIALS AND METHODS

In order to test both safety and effectiveness, the following studies were performed subsequently.

Six fresh human temporal bones were used to test ease of insertion, electrode flexibility, tissue damage, insertion depth, and modiolus proximity. Both the universal and the standard Clarion electrodes were used with and without the positioner. Both electrodes were inserted repeatedly. With the electrode and the positioner in place, the bone over the scala vestibuli was removed and the basilar membrane and the adjacent structures were inspected and dissected for histologic examination.

For the animal study, a modified universal electrode array adapted to the size and shape of the cat cochlea was inserted in the scala tympani, and the electrical auditory brain stem response (EABR) thresholds were measured in the bipolar mode. The measurements were repeated after the insertion of the positioner. The difference in threshold was calculated for each pair of adjacent electrodes. In addition, 10 cats were implanted chronically over a period of 3 months. The cochleas were taken for microdissection and histologic examination.

In 5 adult human patients who had received the standard Clarion 1.2 electrode, the positioner was inserted either before or after electrode placement, and it was left in place permanently in 4 patients. Electrophysiology was performed by means of EABR, stapedius reflex, and impe-



Fig 3. Modified insertion tool for positioner placement.

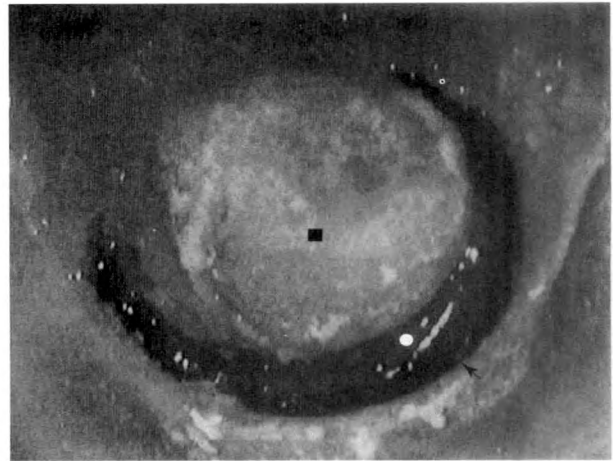


Fig 4. Human temporal bone with basal turn opened, with view from above onto basilar membrane. Standard Clarion electrode (white dot) is pushed toward modiolus (cube) by inserted positioner (arrowhead).

dance measurements with and without the positioner. Plain x-rays were taken to demonstrate the electrode position. The positioner was inserted with different types of tools, including the modified insertion tool.

RESULTS

In the cadaver study, the insertion was easier when the positioner was inserted in a second procedure after electrode insertion. The universal electrode showed excellent insertion properties and flexibility with directional preponderance. The electrodes were always located at the modiolus. The cochleostomy is similar in size to the one used with the standard Clarion electrode array and is oval in shape with a larger diameter in the superior-inferior direction. The modified insertion tool allows for relatively easy insertion of the positioner and helps push the electrode toward the modiolus to locate the positioner exactly at the outer wall of the electrode array. This is true for both the universal and the standard Clarion electrode arrays (Fig 4).

Although multiple reinsertions were performed, no substantial damage to the scala tympani structure, the basilar membrane, or the modiolus could be observed with or



Fig 5. Postoperative plain radiograph in transorbital view, showing standard Clarion electrode with positioner. Shows deep insertion with modiolus proximity.

without the positioner in place. The positioner slid gently and easily along the lateral wall of the scala tympani. The insertion depth could be increased from 360° to 460° without the positioner to about 520° to 620° with the positioner.

In the animal study, the insertion of both electrode and positioner was easy to perform with an angle of about 360°. The EABR thresholds dropped by 6 to 12 dB with the positioner. The long-term studies showed no threshold changes over time. The dissection revealed no or minimal signs of damage to the basilar membrane and no damage to the modiolus. The electrode and positioner were covered with a thin sheet of connective tissue comparable to that found with the standard Clarion electrode. X-ray analysis demonstrated modiolus proximity.

In patients, the cochleostomy must be wide enough to allow insertion of both positioner and electrode into the cochlea. The insertion of the positioner is relatively easy with the modified insertion tool. Half of the electrode was inserted in the human study. The positioner should not mask the lateral contacts of the electrode array, which can be easily controlled with impedance measurements. X-rays show deeper insertion and modiolus proximity with the positioner (Fig 5). The average insertion angle was shifted from around 400° to 560°. The average diameter of the electrode array in the basal turn was 6.1 mm (5.7 to 6.3 mm), compared with 6.8 (6.1 to 7.4 mm) in a group of Clarion patients without the positioner. The impedances increased, whereas the thresholds for EABR and stapedius reflex decreased (for details, see Lenarz et al³).

DISCUSSION

The universal electrode with the positioner is a relatively safe, reliable design for achieving modiolus proximity without running the risk of additional cochlear damage. The cadaver study showed the ease of the insertion and a lack of damage to cochlear structures. The directional preponderance guarantees the correct orientation

of the electrodes' contacts toward the modiolus. A surgical procedure could be established that is largely similar to the insertion of the standard Clarion 1.2 electrode. The universal electrode can also be used without the positioner and would allow soft surgery.⁶ The positioner can also be used for the standard Clarion electrode array. The reliable modiolus proximity, demonstrated by intraoperative x-rays, has functional benefits.³ The lower threshold indicates a smaller distance to the ganglion cells and a more focused current spread in the cochlea.⁴ However, the possibly improved channel separation must be proved in channel interaction studies. The lower thresholds will, in fact, result in lower power consumption.

CONCLUSION

This composite electrode concept provides reliable positioning close to the modiolus with specific electrophysiological properties. These properties may become important for newly designed and future speech-processing strategies.⁷

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NOVEL INTRACOCHELEAR ELECTRODE POSITIONER: EFFECTS ON ELECTRODE POSITION

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Spiral ganglion cells, located in the cochlear modiolus, are widely thought to be the neural elements stimulated by cochlear implants (CIs). Positioning CI electrodes adjacent to the modiolus may allow delivery of more focused, discrete fields of electrical stimulation, reducing both current requirements and the channel interaction associated with simultaneous stimulation. In order to provide greater consistency in positioning CI electrodes against the modiolus, Advanced Bionics Corporation has designed a silicone intracochlear positioner that is inserted alongside the electrode. Placed against the outer wall of the scala tympani, it directs the electrode array toward the modiolus. Five fresh-frozen temporal bones were studied to validate enhanced electrode placement. Electrode position was documented with image-enhanced digital fluoroscopy, and the distance to the modiolus was measured with computer-assisted morphometrics. The electrode positioner was highly effective in positioning the electrodes closer to the modiolus ($p < .001$).

INTRODUCTION

Improvements in cochlear implant (CI) speech processing over the last decade have significantly enhanced hearing and speech outcomes. However, little has changed in

the design or function of CI electrode arrays. Because it is widely thought that the spiral ganglion cells are the elements of the auditory periphery most commonly stimulated by CIs, positioning electrodes adjacent to the modio-



Fig 1. Fluoroscopic image of temporal bone specimen.

lus has theoretical advantages. Among these, it may be possible to reduce the current levels required for adequate auditory stimulation. This may reduce the possible damage to the remaining spiral ganglion cells by electrical current, and it may allow a reduction in battery size, which is an important consideration in ear-level wearable speech processors. It may also be possible to increase stimulus selectivity by allowing the delivery of more focused and discrete fields of electrical stimulation.

A novel silicone intracochlear positioner (Advanced Bionics Corporation, Sylmar, Calif) has been designed to be used in conjunction with the Clarion intracochlear electrode array. The aim of this study was to determine the effect of this positioner on CI electrode position in relation to the modiolus.

MATERIALS AND METHODS

The study was conducted on 5 fresh-frozen adult human temporal bones. With the use of videofluoroscopic imaging and computer morphometrics, distances between electrodes and the modiolar wall were determined. Distance measurements were taken under 2 conditions: 1) with a fully inserted electrode array and 2) with a silicone positioner inserted alongside the electrode array.

The temporal bones were dissected by means of surface preparation techniques. Bone was removed until the scala tympani was skeletonized but intact. A cochleostomy into the basal scala tympani was created anterior-inferior to the round window membrane. Each specimen was then mounted on a cardboard frame with a window cutout to accommodate the specimen.

With the use of a technique similar to that first described by Fishman et al,¹ each temporal bone specimen was imaged on the XiScan 1000 Track Mounted C-arm Fluoroscopic System (XiTec Incorporated). Image clarity was optimized by applying an image enhancement system that mathematically averaged a group of 16 captured frames. Hard copies of the fluoroscopic images (Fig 1) were generated from the built-in thermal printer (Mitsubishi P90U video copy processor), as well as on standard VHS videotape.

Each temporal bone specimen was kept hydrated in normal saline before electrode insertion. Hyaluronic acid (Healon, Pharmacia & Upjohn, Kalamazoo, Mich)² was injected through the cochleostomy until the scala tympani was filled. Under microscopic visualization, a Clarion intracochlear electrode array was then inserted in the standard fashion with the electrode insertion tool. After imaging, the silicone intracochlear positioner was then inserted into the scala tympani along the outer perimeter of the spiral electrode array. This was accomplished with the combined use of a positioner insertion tool and other instruments.

The peripheral bony margin of the modiolar wall was precisely traced on a clear plastic sheet. The tracing was overlaid on images of identical magnification in both implanted conditions (Fig 2). This step is required because once the electrode is inserted, the edge of the modiolus is difficult to visualize.

Each composite image was then scanned into a Macintosh PC with the Adobe Photoshop program. Morphometric analysis was then conducted with the NIH Image program. Measurements on each image were calibrated from the known distances between electrodes 1L and 2L (2.0 mm) and between electrodes 1M and 2L (1.5 mm), used as references. The distance of each electrode to the modiolus was determined by measuring the shortest distance from the electrode to a point on the modiolus.

Data were analyzed statistically with the paired *t*-test

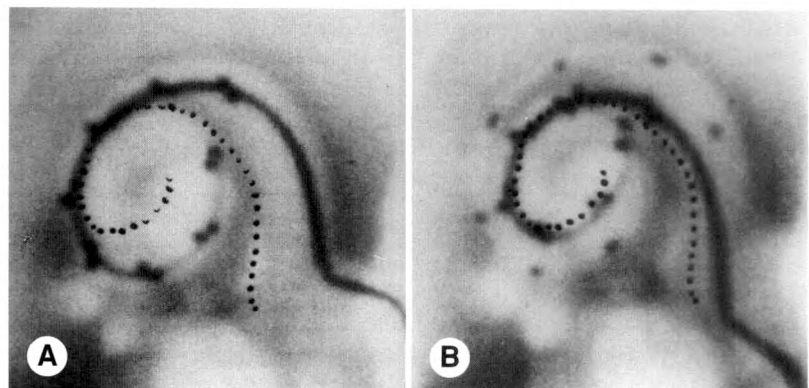


Fig 2. Temporal bone image with superimposed modiolar wall template. A) With fully inserted electrode array. B) With silicone positioner inserted alongside electrode array.

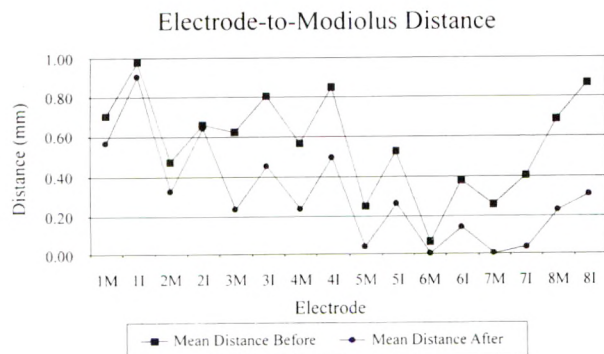


Fig 3. Mean electrode-to-modiolus distance for each electrode before and after insertion of silicone positioner.

and the F-test for equality of variance.

RESULTS AND DISCUSSION

Methods used to determine intracochlear electrode position both in the temporal bone model and in clinical practice have been previously described. These include the use of conventional radiography, high-resolution computed tomography (CT) scans, and 3-dimensional CT reconstructions.³⁻⁵ We have found that videofluoroscopy can be useful in the assessment of intracochlear electrode position in *in vitro* studies. When videofluoroscopy is used to visualize properly prepared temporal bone specimens, it is possible to obtain both real-time video and fixed images of intracochlear anatomy and electrode array insertion of remarkable clarity.

The mean electrode-to-modiolus distances for each electrode measured before and after insertion of the silicone positioner are shown in Fig 3. It can be seen that there is an overall decrease in distance, with the greatest

changes occurring at electrode pairs 3, 4, 7, and 8. The mean electrode-to-modiolus distance for all electrodes combined was 0.56 mm before placement of the positioner, and 0.26 mm after positioner insertion. The mean change in distance for all electrodes was 0.24 mm, and this was found to be statistically significant ($p < .001$). It was also observed that a statistically significant variation ($V = 0.15$, $p = .013$) in the electrode-to-modiolus distance across electrode arrays was present without the positioner. This variation, however, became insignificant with the positioner in place. These results indicate that the silicone positioner allows the electrodes to be placed adjacent to the modiolus with greater consistency than they can be with the use of the electrode array alone.

Future studies on impedance changes, as well as histopathologic studies to determine the degree of insertional trauma, related to the use of the positioner need to be undertaken.

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PRINCIPLES AND OUTCOME IN PERIMODIOLAR POSITIONING

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MATERIALS AND METHODS

Modeling and animal electrically evoked auditory brain stem response (EABR) data indicate that an electrode array positioned against the inner wall of the scala tympani will produce a lower threshold and a higher dynamic range while reducing channel interaction.¹⁻⁴ Patient performance should improve.⁵ The cardinal difficulty in all electrode placements is caused by the 2-to-1 ratio in outer to inner wall length and by the spiraling geometry of the scala.^{6,7} If a straight array is fully inserted along the outer wall (33 mm for the implant with the longest insertion depth), the positioning principally involves a significant retraction of the electrode out of the scala. A simple radial translation of the electrode from the lateral to the medial wall is excluded.

This paper presents a perimodiolar electrode prototype.

The electrode design is based on the Med-El Combi-40+ multichannel implant.⁸ During surgical insertion, the electrode array conforms to the outer wall of the fluid-filled scala tympani. The prosthesis incorporates a longitudinal microgroove molded near the edges of the electrode carrier (Fig 1). A single wire made of nitinol, 100 μ m in diameter and 4.5 cm in length, is embedded in the microgroove. Nitinol is a biocompatible alloy composed essentially of 50/50 nickel-titanium. The strand of metal has superelastic characteristics and is widely used in the medical industry.⁹ The apical end of the wire is fixed in a molded silicone notch at the apical end of the carrier. The basal end of the rod may slide through a short silicone tunnel molded inside the microgroove. The design precludes the use of banded electrode contacts.

After insertion of the electrode carrier into the cochlea,

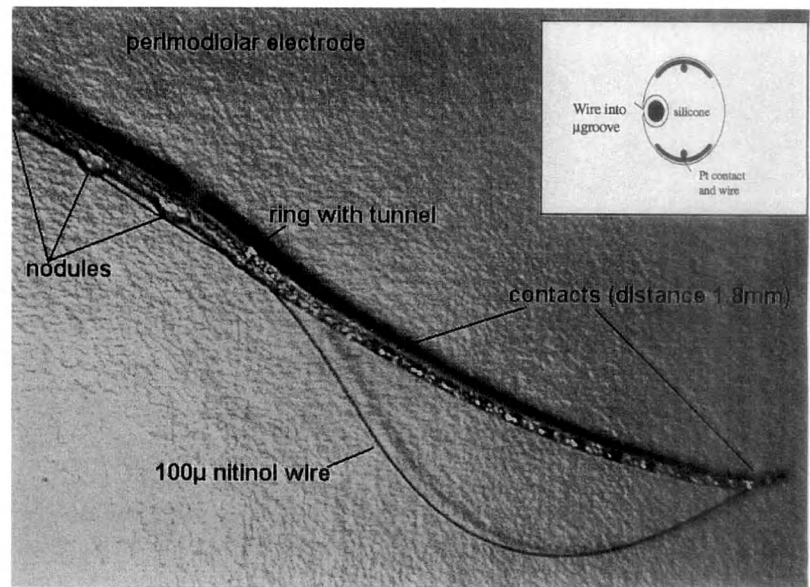


Fig 1. Cross section of electrode array and engineering. Twelve-channel array is shown with 100- μ m wire arched out of microgroove.

the wire or rod is held stationary, posterior to the cochleostomy, by the surgeon. The electrode is then gently retracted. This slight pulling of the array out of the cochlea separates the inner wire from the carrier's microgroove, except at the apex, where the rod fits into a silicone cavity. The surgeon's continued retractile motion on the electrode carrier causes the array to wrap around the inner wall of the cochlea. The retractile positioning is referred to as the Innsbruck positioning technique. Key to the technique is the synergy between the superflexible but not plastically deformable wire and the flexible but plastically deformable electrode.

RESULTS

Figure 2 shows the electrode in vitro as it appeared

while the repositioning technique was applied in an approximate cochlea model. The series of photos were taken with a dental x-ray apparatus. The model was built by forming a loop with a high-density porous polytetrafluoroethylene tube 2 mm in diameter (International Polymer Engineering, Tempe, Ariz). The base of the loop is 1 cm in diameter. Both the inner wall and outer wall of the tube can be seen in the sequence. A small kink is present on the inner wall of the compressible tube.

The electrode array was initially inserted 30 mm against the outer wall of the model. This distance corresponds to the length of the cochlea covered by the best insertion depth.¹⁰ In Fig 2A, the lower left corner mark corresponds to the tube entrance. Figure 2B,C shows that when the 100- μ m nitinol wire is held still with a pair of forceps

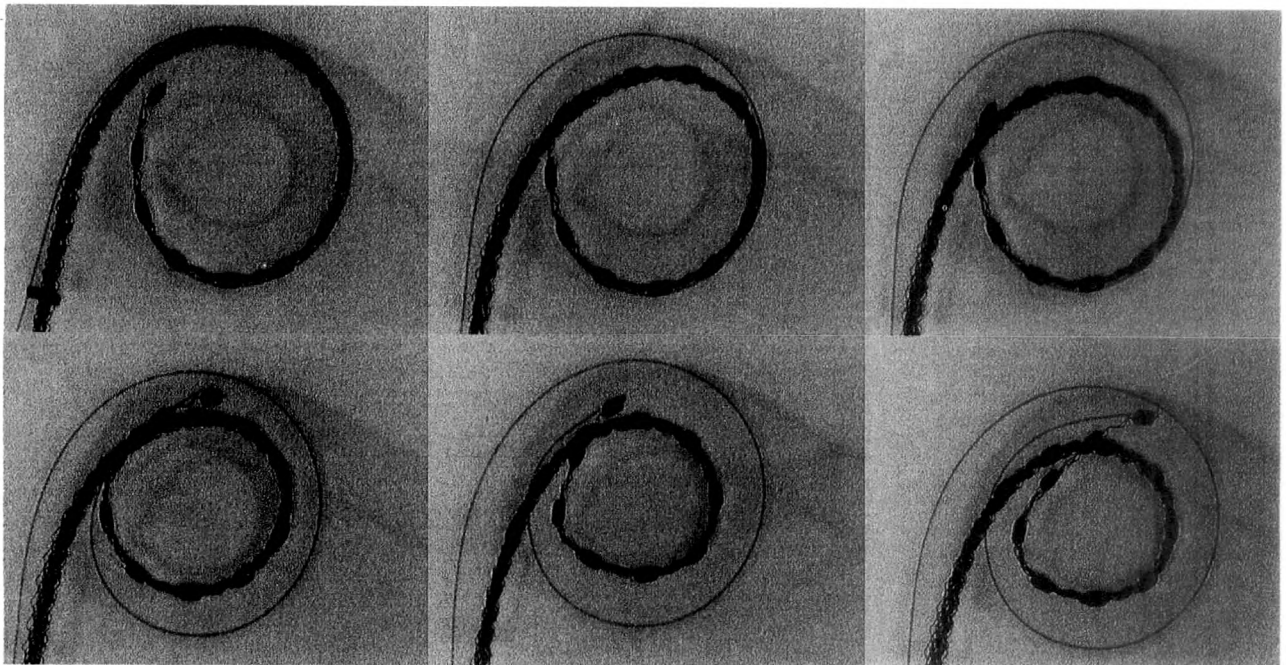


Fig 2. X-ray sequence of positioning technique in vitro (see text for details).

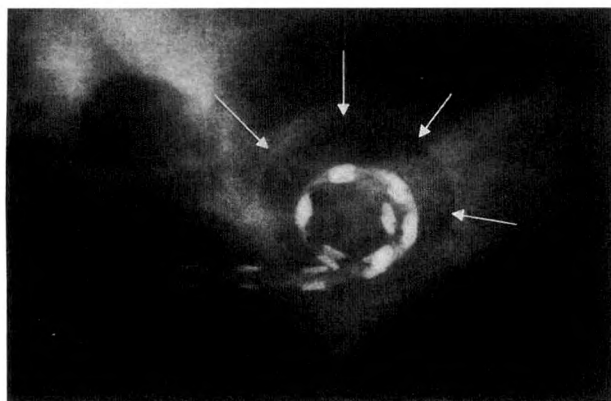


Fig 3. X-ray of temporal bone after positioning of electrode. Arrows outline shadow of 100- μ m nitinol wire. Electrode spacing is 1.8 mm.

and the electrode array is slowly withdrawn from the tube, the tip of the electrode remains stationary during the pullback. Between Figs 2C and 2D, the nitinol wire was pushed in an extra 4 mm to gain some more insertion depth. From Fig 2D to 2F, the array continues to move closer to the inner wall of the tube as the electrode is pulled back. Again, the tip of the array is essentially stationary. In the last photograph (Fig 2F), the array is in apposition with the inner wall, except for 2 mm at the apical end. The 100- μ m wire is arched against the outer wall, except at 1 basal point and 1 apical point, where it coalesces with the silicone carrier. The distance between the array and the wire is 2 mm, as can be judged by the 1.8-mm inter-electrode spacing. Interestingly, the array adopts the contour of the tube's inner wall even where a small kink exists in the tube. For the electrode to adopt the contour of the tubing inner wall, it had to be retracted approximately one third (10 mm). Explantation was achieved by first disconnecting the apical tips of the electrode and wire. The disconnection is achieved by holding the electrode firm and pulling back on the superflexible wire. The wire is then removed from the lumen, followed by the electrode.

The novel array was tested in fresh temporal bones. After mastoidectomy and posterior tympanotomy, a cochleostomy 1.2 mm in diameter was drilled. The array was inserted with the microgroove and wire facing the lateral wall. A lubricant was used to facilitate insertion. The insertion depth to the point of first resistance was between 20 and 30 mm. Repositioning was applied in situ: the nitinol wire was held fixed at the cochleostomy with forceps, and the silicone matrix forming the electrode array was slowly and gently retracted until resistance was met. Resistance takes place when the electrode surrounds and hugs the modiolar wall. The electrode retracted length is between 7 and 10 mm and correlates with insertion depth. Experience has shown that one third of the inserted electrode length is retracted during repositioning. In one x-ray image (Fig 3), the array is shown lying against the modiolar wall for more than 1 turn (electrode spacing = 1.8 mm). A shadow caused by the wire is visible in the basal turn of the cochlea. The distance between the array and the wire seems greater than 1.5 mm in a significant portion of the basal turn.

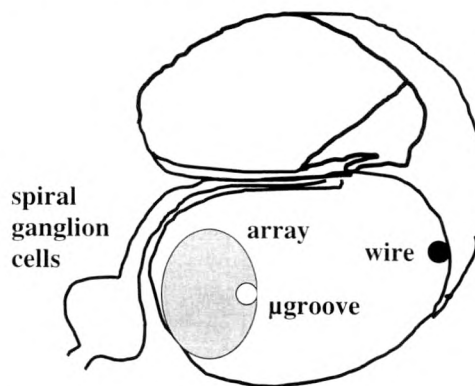


Fig 4. Cross-sectional sketch of basal turn of cochlea with array and wire in position.

Other data show that the Innsbruck positioning technique was successful in positioning the array against the medial wall even when the electrode was inserted for half a turn. An added advantage to the system is that the array is anchored in the scala. Such anchoring is provided by the arching of the silicone and wire. Both arches coalesce securely at the apex and at the constriction formed by the cochleostomy.

From the surgeon's point of view, the force deployed during the retractile positioning is unsubstantial until the array completely hugs the medial wall. It is assumed that the positions of the wire and electrode and the orientation of the microgroove will be as shown in Fig 4. The tendency of the wire and electrode will be to maximize their separation.

Several cochleas have been fixed in epoxy for further sectioning with the array in situ. Histologic data will confirm the trauma extent. It is expected that some mechanical trauma will be inflicted upon the spiral ligament by the 100- μ m wire. No trauma is expected to be inflicted on the medial wall of the scala tympani or on the spiral lamina structure.

The positioning paradigm, although counterintuitive, conforms the array to the inner wall of the scala, regardless of cochlear size, insertion depth, and ear side. In vitro and in situ data confirm that the minimally invasive electrode is implantable and explantable. The surgical procedure and cochleostomy size are unchanged.

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SHAW SCALPEL IN REVISION COCHLEAR IMPLANT SURGERY

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The use of traditional electrocautery is prohibited in revision or replacement cochlear implant surgery because of the concern for end organ tissue damage. Additionally, electrical current spread to the malfunctioning device could interfere with an accurate cause-of-failure analysis. Clinical reports have confirmed the utility of the Shaw scalpel for dermatologic, ophthalmic, and head and neck surgery. The Shaw scalpel is a thermally activated cutting blade that provides a bloodless field through immediate capillary and small vessel hemostasis. Avoidance of wound and flap complications is of primary concern in cochlear implant surgery. The long-term wound healing compared favorably to that of other surgical cutting instruments in several experimental reports. We have routinely used the Shaw scalpel in revision cochlear implant surgery and in primary surgery whenever electrocautery was contraindicated. We have retrospectively evaluated 22 cases in which the Shaw scalpel was used for cochlear implant revision and primary surgery. The chart review included patient demographics, the indication for surgery, the contraindication for electrocautery, intraoperative surgical notes, the wound healing evaluation, the evaluation for alopecia, and postoperative speech understanding. No significant complications occurred intraoperatively, and the long-term wound healing results were no different from those obtained with conventional surgical techniques. The explanted devices were undamaged, and valuable diagnostic information could be obtained. All patients performed at or better than their preoperative levels on speech recognition testing. Our results indicate that the Shaw scalpel is a relatively safe, easy-to-use, and effective instrument.

INTRODUCTION

Two conditions exist in which electrocautery may be contraindicated in cochlear implant patients: 1) revision and other head and neck surgery in a patient with a cochlear implant and 2) primary cochlear implantation in a patient with another electronic medical device. Electrocautery instruments are used in nearly all surgical procedures. Monopolar devices rely on electrical current passing from a small-tipped, handheld instrument to a large

grounding pad applied to the patient at a distance from the operative field. Heat generated at the tip enables vessel coagulation for hemostatic purposes. In a bipolar device, the current only passes between 2 points at the instrument tip. Current spread through or near an implanted medical device could damage the device, cause device discharge, cause device heating, and potentially damage the organ or tissue to which the device is attached.

The use of electrocautery in the patient with a cochlear implant is potentially harmful to the patient and the device. Current spread through the device would undoubtedly cause changes in the device settings and possibly cause permanent device damage. Severe morbidity has occurred in pacemaker patients when electrocautery was used during a procedure.^{1,2} Additionally, the transmission of current and heat to the spiral ganglion cells might have severe obvious consequences. It is for these reasons that all electrocautery machines are turned off and disconnected from the patient once the device is brought onto the sterile field during primary cochlear implant surgery. Fortunately, all needs for hemostasis have been satisfied at the point in the operation when device electrode insertion occurs.

In performing revision cochlear implant surgery and other head and neck surgery in patients with cochlear implants, an alternative to electrocautery must be used for hemostasis. Possibilities include standard clamp and tie techniques, bipolar electrocautery, laser, and the Shaw scalpel. The Shaw heated scalpel (Hemostatix Medical Devices) can provide better hemostasis than a regular sharp scalpel without the transmission of current to the patient (Fig 1). This device utilizes a sharp heated cutting



Fig 1. Shaw scalpel consists of Teflon-coated regular-size 15 or 10 blade with microcircuitry that is attached to handle with controls for increasing and decreasing temperature. Additional control on superior knife surface provides surge to increase temperature for larger-vessel coagulation. Handle is connected to control box by way of wire cable. Adjustable current passes through blade, causing heating without current's passing into patient.

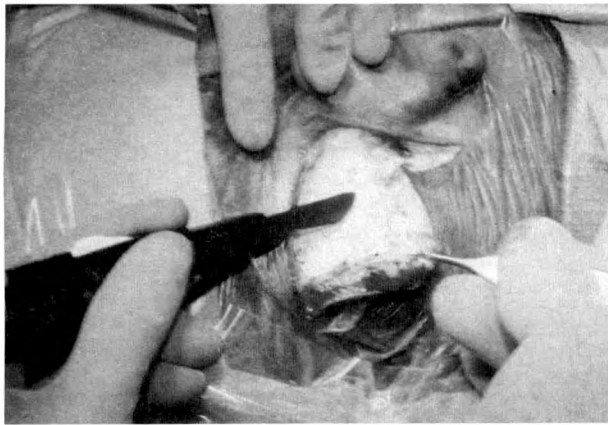


Fig 2. Bloodless incision is made and posteriorly based postauricular flap is raised with Shaw scalpel.

blade for simultaneous cutting and coagulation (Fig 2). Histologic analysis of wounds caused by any device that generates heat has shown delays in the early phases of healing without complications or ultimate reduction in strength.^{3,4} Several reports attest to the safety and lack of wound healing complications with the Shaw heated scalpel.^{3,5}

To evaluate the effects of the Shaw scalpel on wound healing and on patient and device outcome, we retrospectively reviewed cases in which electrocautery was contraindicated and the Shaw scalpel was used.

MATERIALS AND METHODS

A chart review was conducted on the 400 cochlear implant recipients fitted with implants at the New York University Medical Center Cochlear Implant Program. The study population consisted of 22 patients in the following groups: 17 patients were identified who underwent revision or reimplantation cochlear implant surgery, 1 patient underwent device removal, 1 patient was reoperated for a cerebrospinal fluid leak, 1 patient had an acoustic neuroma removed from the side opposite an existing cochlear implant, 1 patient had cochlear implantation performed

in the side opposite an auditory brain stem implant, and 1 patient had a pacemaker in place. The Shaw scalpel was used in place of electrocautery in all patients in the study population.

Patient demographics, indication for surgery, length of time from original implantation until second surgery, contraindication to electrocautery, explanted device, implanted device, postoperative wound healing, and evaluation for alopecia were recorded. Wound healing was recorded as either delayed or normal. Alopecia was recorded as either present or absent. Postoperative speech understanding scores were recorded as the same as, better than, or worse than the preoperative levels. Postexplantation cause-of-failure analysis was recorded as either possible or not possible. Additionally, the intraoperative surgical and nursing notes were reviewed for mention of unusual complications and blood loss.

RESULTS

The results of this retrospective analysis are presented in the Table. There were no wound healing delays, and alopecia was not observed. The cause-of-failure analysis was obtainable in all applicable cases. The speech understanding results were the same as or better than the preoperative results in all 22 patients. A cause-of-failure result of "not applicable" relates to patients with older Ineraid and House 3M single-channel devices, in whom no failure analysis was conducted or no device was explanted. Patient 10 was operated on to reposition an electrode array that was originally placed in an extracochlear position at another institution. She had severe cochlear dysplasia. Patient 17 had a pacemaker. Patient 18 had neurofibromatosis type 2 and a nonfunctioning auditory brain stem implant on the opposite side. Patient 20 had acoustic neuroma surgery on the side opposite a well-functioning cochlear implant. Patient 22 was reexplored for a cerebrospinal fluid leak after cochlear implantation. She also had severe cochlear dysplasia. In all cases, a review of the operative notes and nursing notes failed to reveal complications, and subjectively, blood loss was minimal.

RESULTS

	Patient Number																					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Age (y)	36	34	64	72	62	68	3	7	3	5	3	12	53	43	5	38	73	53	11	36	43	2
Sex	M	F	M	M	M	M	M	F	M	F	F	M	F	M	F	F	M	F	M	F	F	F
Cause of deafness	U	U	U	O	T	U	C	CMV	C	C	C	U	O	U	CMV	T	O	NF2	C	RAN; LU	M	C
Reason for surgery	F	F	I, U	U	F, U	I, U	F	F	F	RP	F	F	F	F	F	F	1°	1°	F	1°	F, U	CSF
Time from implant to 2nd surgery (y.mo)	10.2	6.11	7.11	8.6	8.1	6.9	4.4	4.6	1.8	0.5	0.2	0.3	0.1	0.4	0.3	9.0	NA	NA	0.3	NA	1.8	0.5
Contraindication to electrocautery	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	P	ABI	D	D	D	D
Failure analysis	+	+	NA	NA	NA	NA	+	+	+	NA	+	+	+	+	+	+	NA	NA	+	NA	NA	NA
Speech result	0	+	+	+	0	+	0	+	+	+	+	+	+	0	+	0	+	+	+	+	+	+
Explanted device	N22	N22	IN		3M	IN	N22	N22	N22		N22	N22	N22	N22	N22	N22			N24		3M	
Implanted device		N22	N22	N22	N22	N22	N22	N22	N22		N22	N22	N22	N22	N22	N22	N22	N24	N24		N22	

Wound healing was normal (not delayed) in all patients, and alopecia was absent.

Causes of deafness: U — unknown, O — otosclerosis, T — ototoxicity, C — congenital, CMV — cytomegalovirus, NF2 — neurofibromatosis type 2, AN — acoustic neuroma, M — meningitis. Reasons for surgery: F — failure, I — infection, U — upgrade, RP — reposition, 1° — primary surgery, CSF — CSF leak. Contraindications to electrocautery: D — device, P — pacemaker, ABI — auditory brain stem implant. Failure analysis: + — analysis possible, NA — not applicable. Speech results: 0 — unchanged, + — improved. Explanted/implanted devices: N22 — Nucleus 22, IN — Ineraid, 3M — House 3M single-channel, N24 — Nucleus 24M.

DISCUSSION

Concerns about electrocautery-induced damage and the need for hemostasis led to the utilization of the Shaw scalpel in revision cochlear implant surgery. The original surgical wounds were reopened in all revision cases, and standard surgical approaches were used in the other cases. Subjectively, we have found this instrument to be easy to use with only slight modifications in surgical technique over the use of a regular scalpel blade. Surgery on the acoustic neuroma patient did not require more time because of the lack of electrocautery availability, and total blood loss was no different from that in other, similar procedures.

Because the blade temperature is adjustable and can reach a maximum temperature of 280°C, the surgeon should use caution when working near important structures. This is especially prudent in very young children, in whom the facial nerve is in a more superficial position near the mastoid tip. The use of the Shaw scalpel was found to be a significant risk factor for facial nerve weakness in primary parotid surgery.⁶ The heat generated from the electrocautery is of similar risk in regions in which the facial nerve is in close proximity. Heat generated in the blade might also melt the silicone covering of some cochlear implants, and therefore the heated blade should not contact the device. Interestingly, one report in the literature outlines the advantages of using the Shaw scalpel to achieve a smooth contour in carving silicone blocks for various implants.⁷

All explanted devices are returned to the factory for cause-of-failure analysis. There was no evidence of further thermal or electrical device damage from the explantation process in the returned devices. Electrical current

or mechanical forces might further damage an explanted device, preventing the acquisition of helpful analysis information.

There was no evidence of damage to the spiral ganglion cells or their central projections in this study. All patients tested at levels equivalent to or better than their preoperative performance. Any instrument that has the potential to damage the neural elements of the auditory system should be avoided in primary and secondary cochlear implant procedures.

CONCLUSION

The Shaw scalpel is a relatively safe and effective instrument for revision cochlear implant surgery and for use in patients with other implanted medical devices.

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MASTOIDITIS AND ACUTE OTITIS MEDIA IN CHILDREN WITH COCHLEAR IMPLANTS: RECOMMENDATIONS FOR MEDICAL MANAGEMENT

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Acute otitis media (OM) or mastoiditis is a very dangerous condition for the ear after cochlear implantation. However, acute OM is very common in childhood and can occasionally occur in an implanted ear. Most cases of acute OM can be successfully treated with intravenous high-dosage antibiotics. In cases of mastoiditis and clinical signs of mastoid abscess, retroauricular drainage is necessary to prevent infection of the implant bed. In a series of 366 children given implants (1 to 14 years), acute OM occurred in 5.6% during a follow-up period of 1 to 8 years. Seven ears had to be opened by means of myringotomy. Five ears were opened by retroauricular incision with mastoid revision on the implanted side. Adenoidectomy and use of ventilation tubes before cochlear implantation, as well as careful subtotal mastoidectomy during the implantation, can reduce the incidence of acute OM in children after implantation. Early and subsequent treatment with operative mastoid drainage can prevent implant loss and should be performed at the implantation center.

INTRODUCTION

Over a period of more than 12 years, cochlear implantation has been performed in more than 1,250 patients at the Department of Otolaryngology, Medical University of Hannover. In most cases, a Nucleus device (Cochlear Pty Limited, Lane Cove, Australia) was used. For the last 4 years, the intracochlear Clarion device (Advanced Bionics) has additionally been used in children, as well as in

adult patients.¹ Complications in cochlear implantation are defined as minor (no or conservative treatment), major (revision surgery, meningitis, implant loss, facial nerve injury), intraoperative (gusher, obliteration), early (immediately and up to 3 months after surgery), and delayed (more than 3 months after surgery, eg, cholesteatoma, electrode dislocation, device failure). For this investigation, we evaluated the rate and outcome of severe postimplan-

TABLE 1. INFECTIOUS COMPLICATIONS AFTER COCHLEAR IMPLANT SURGERY

Complication	Children (n = 366)		Adults (n = 331)	
	No.	%	No.	%
Meningitis	0	0	0	0
Acute otitis media	20	5.5	5	1.5
Severe infection with explantation	2	0.5	3	0.9
Cholesteatoma	1	0.25	19	5.7
Mastoiditis	5	1.25	7	2.1
Labyrinthitis	1	0.25	3	0.9

tation infections that could be related to acute otitis media (OM) and/or mastoiditis.

MATERIALS AND METHODS

For this study, we investigated the clinical records of 366 children who were operated on between 1987 and 1997 in Hannover. Their ages ranged from 1 to 14 years. In most of the cases, a Nucleus 22 mini implant was used. Additionally, since 1994, the Clarion 1.2, and since 1997, the Nucleus 24M, devices have been implanted in children at our department. Most of the children lost their hearing because of meningitis (n = 200) or were congenitally deaf. Additionally, the data on infectious complications of 331 adult cochlear implant patients were included so that we might compare the incidence of infectious complications in children and adults.

RESULTS

During the follow-up period of up to 8 years, acute OM occurred in 11 children on the implanted side and in 9 children on the contralateral side, resulting in a rate of 5.6%. Seven ears were opened by means of myringotomy. Five ears were opened by means of a retroauricular approach, and in all of them, acute mastoiditis with pus was found. In these cases, scar tissue and thickened mastoid mucosa was removed. The antrum was reopened and a small drainage tube was inserted and kept in place for up to 5 days. No further complications occurred during follow-up. In 1 girl, labyrinthitis with loss of implant performance was observed after rubella vaccination. The reimplantation procedure was complicated by severe ossification of the implanted cochlea. In 2 additional cases, severe infection in the implant bed developed, and despite local and conservative treatment, the devices had to be removed (Table 1). The electrode was left inside the cochlea. In 1 case, successful reimplantation was performed 1 year later. In the second child, reimplantation was performed in the summer of 1998 without further problems.

DISCUSSION

In our opinion, cochlear implantation is a relatively safe and reliable otosurgical procedure. The rate of severe complications is low as compared to other surgical procedures. Comparing our data² to the multicenter study of Hoffmann and Cohen,³ we find that the same range of complications occurred (Table 2). The low rate of severe complications is related to several issues. In Hannover, a stan-

TABLE 2. COMPARISON OF COMPLICATION RATES IN PEDIATRIC COCHLEAR IMPLANTATION

	Hoffman and Cohen ³ (n = 1,905)		Hannover, <3 mo (n = 366)		Hannover, >3 mo (n = 366)	
	No.	%	No.	%	No.	%
Flap complications	30	1.57	10	2.73	1	0.27
Electrode dislocation	25	1.31	0	0	1	0.27
Facial nerve stimulation	18	0.94	4	1.09	7	1.91
Facial nerve injury	11	0.58	0	0	0	0
Electrode malinsertion	11	0.58	0	0	0	0

dard surgical procedure for all patients is used by a small number of surgeons. However, because of the large number of patients, cochlear implantation is a routine surgical procedure and a complete program involving the whole team.⁴⁻⁶ Major postoperative problems — wound infections, flap problems, electrode dislocation — should be treated with special techniques^{4,7,8} to avoid explantation and intracranial complications. On the other hand, infectious complications related to acute OM occur more frequently in children than in adults (Table 1).

Acute otitis media or acute mastoiditis in the implanted ear should be treated as promptly as in unimplanted ears. Antibiotics should be administered intravenously and a few days longer than normal. The mastoid can also be opened without risk to the implant, as reported by Marangos et al⁹ and proved by our own experience. In cases of severe infection, removal of the device is necessary and provides the only chance of healing. The electrode should remain in the cochlea, thus keeping open the intracochlear space. As shown in the reported cases, a successful reimplantation on the affected side is possible, eg, after 1 year.

Adenoidectomy and use of ventilation tubes before implantation, as well as careful subtotal mastoidectomy during cochlear implant surgery, can probably reduce the incidence of acute OM in children after implantation. During the preimplantation investigation in children, we routinely examine the nasopharynx and remove the adenoids. In cases of serous OM, grommets are inserted to improve ventilation of the middle ear spaces.⁵ In cases of chronic mastoiditis detected during cochlear implant surgery, we recommend subtotal mastoidectomy without implantation. In a second-stage surgery, implantation can be performed after 6 months under improved mastoid conditions.

In conclusion, as expected for a pediatric population, acute OM and mastoiditis can occur in the implanted, as well as the contralateral, ear. Early detection, consequent conservative treatment, and, if necessary, operative opening of the mastoid can prevent infection of the device bed with subsequent implant loss.

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COCHLEAR IMPLANTATION IN JERVELL AND LANGE-NIELSEN SYNDROME

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Jervell and Lange-Nielsen syndrome represents a rare, autosomal recessive cause of congenital deafness. Affected patients have a characteristic prolongation of the QT interval on electrocardiogram, along with cardiac arrhythmias, recurrent syncopal episodes, and a predisposition to sudden death. We present the first reported case of cochlear implantation in a child with Jervell and Lange-Nielsen syndrome. Special perioperative precautions were required, including cardiac monitoring for 48 hours, perioperative beta blockade, and special anesthetic considerations. Because sudden patient death has been associated with exposures to loud sounds in patients with prolonged QT syndrome without hearing loss (Ward-Romano syndrome), initial cochlear implant stimulation was performed with cardiac monitoring. This patient has responded well to cochlear implantation with 11 months of implant use. The patient has achieved limited open-set word comprehension and significantly improved speech, as is expected for her age. Although the patient had no problems with cardiac arrhythmias at surgery, she has since experienced a syncopal episode requiring placement of an automatic pacemaker and defibrillator. The implant has continued to work well despite the pacemaker and defibrillator. Cochlear implantation can be relatively safely performed in patients with Jervell and Lange-Nielsen syndrome, provided proper precautions are followed.

INTRODUCTION

Jervell and Lange-Nielsen syndrome (JLN) is a rare autosomal recessive condition characterized by congenital deafness, prolongation of the QT interval on electrocardiogram, cardiac arrhythmias, syncopal episodes, and sudden death.^{1,2} The arrhythmias may occur in response to emotional or physical stress and are thought to be an explanation for cases of sudden death at schools for the deaf.³ An implantable automatic defibrillator may prove life-saving in preventing sudden death.⁴

The syndrome is thought to occur as a result of a mutation on the potassium channel gene (KVLQT1) on chromosome 11 or the ISK gene that encodes 2 components of the rectifier potassium channel on chromosome 11.⁵ In the heterozygous, autosomal dominant form (Ward-Romano syndrome), there is slight elongation of the QT interval without hearing loss.⁶

Temporal bone studies have shown the presence of periodic acid-Schiff-positive hyaline nodules throughout the cochlea and the vestibular portion of the membranous labyrinth and adjacent to the terminal vessels of the stria vascularis.⁷ In situ hybridization studies in mice with mutations of the potassium channel gene (KVLQT1) have shown expression in the stria vascularis, suggesting that this gene is necessary for endolymph homeostasis.⁵

Our experience with a patient with Jervell and Lange-Nielsen syndrome prompted this literature review and case report.

CASE REPORT

A 3¹/₂-year-old girl was the product of a vaginal deliv-

ery at term with induction of labor because of fetal bradycardia. The pregnancy had been otherwise unremarkable. Because of the bradycardia and an episode of cyanosis during feeding, the child was hospitalized in the intensive care unit (ICU) for 7 days. While she was in the ICU, a cardiology evaluation revealed a prolonged QT syndrome. The patient was determined to have Jervell and Lange-Nielsen syndrome and was started on propranolol hydrochloride for beta blockade. An auditory brain stem response (ABR) screening through the hospital's high-risk identification program resulted in a diagnostic hearing evaluation that subsequently confirmed a bilateral profound sensory hearing loss. At 4 months of age, a trial was initiated with power hearing aids. She showed no responses with standard amplification or with tactile stimulation.

The patient's family was encouraged to undergo electrocardiographic screening for prolonged QT syndrome. Tragically, before the child's mother could be screened, she experienced an arrhythmia and died suddenly. It was subsequently found that there was an extensive family history of prolonged QT interval and that there was also consanguinity between the mother and father.

Subsequent computed tomography scanning and cochlear implant evaluation were performed and revealed the patient to be a good candidate for implantation. At 25 months of age, cochlear implantation of a Nucleus-22 channel device in the left ear was performed, with complete insertion of all 22 active electrodes and all 10 stiffening rings. The patient's propranolol was continued perioperatively, and the patient was observed for 48 hours

postoperatively in the ICU. No significant arrhythmias were encountered. Suture removal and initial stimulation were also carried out in a monitored setting. With intensive training, the patient has acquired functional open-set word comprehension and expressive language skills approximately 1.5 years behind those of her hearing peers. The patient experienced a syncopal episode 11 months after implantation and recently underwent placement of an automatic defibrillator and pacemaker. The patient has continued to perform consistently with the implant, with no sign of device malfunction. The automatic defibrillator has not required activation over 3 months of use.

DISCUSSION

Jervell and Lange-Nielsen syndrome represents a rare cause of congenital hearing loss.³ Because of the potential for cardiac arrhythmias and sudden death, additional risks are involved in cochlear implantation. Informed consent in these patients should include these risks, as well as the standard risks of cochlear implant surgery. Multiple cases of arrhythmia and sudden death in response to emotional or physical stress have been documented in Jervell and Lange-Nielsen syndrome. Because of the potential for an excitation-induced arrhythmia, we would advocate initial stimulation of the implant and suture removal in a monitored setting. It is critical to continue propranolol during surgery, because discontinuing the medication may be arrhythmogenic.

The family pedigree for this patient was unusual in that a typical autosomal recessive pattern skipping generations was not seen. This suggests an autosomal dominant pattern. DNA analysis and further electrocardiographic screening of family members will help us to understand the genetic defect in this family.

The abnormality caused in the stria vascularis in mice by *in situ* hybridization of the KVLQT1 gene is of interest.⁵ It would seem likely that the endocochlear potential would be affected by a mutation in a gene affecting potassium homeostasis in the scala media. Further study of a mouse animal model may prove fruitful in determining

the cause of the hearing loss. Schuknecht⁸ has proposed that loss of stria vascularis function may result in a flat sensorineural hearing loss in advanced age as one form of presbycusis.

Concern was raised preoperatively about possible problems with use of both an automatic defibrillator-pacemaker and a cochlear implant. The manufacturer, Cochlear Corporation, Englewood, Colorado, assured us that the localized current of the defibrillator should not have any deleterious effect on function. Although the defibrillator has not been required over the 3 months since it was implanted, the pacemaker has been required and used on several occasions, without any malfunction of the implant.

Jervell and Lange-Nielsen syndrome poses additional concerns for the cochlear implant team, but implantation may be relatively safely performed, provided appropriate precautions are taken.

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FACTORS ASSOCIATED WITH SPEECH INTELLIGIBILITY IN CHILDREN WITH COCHLEAR IMPLANTS

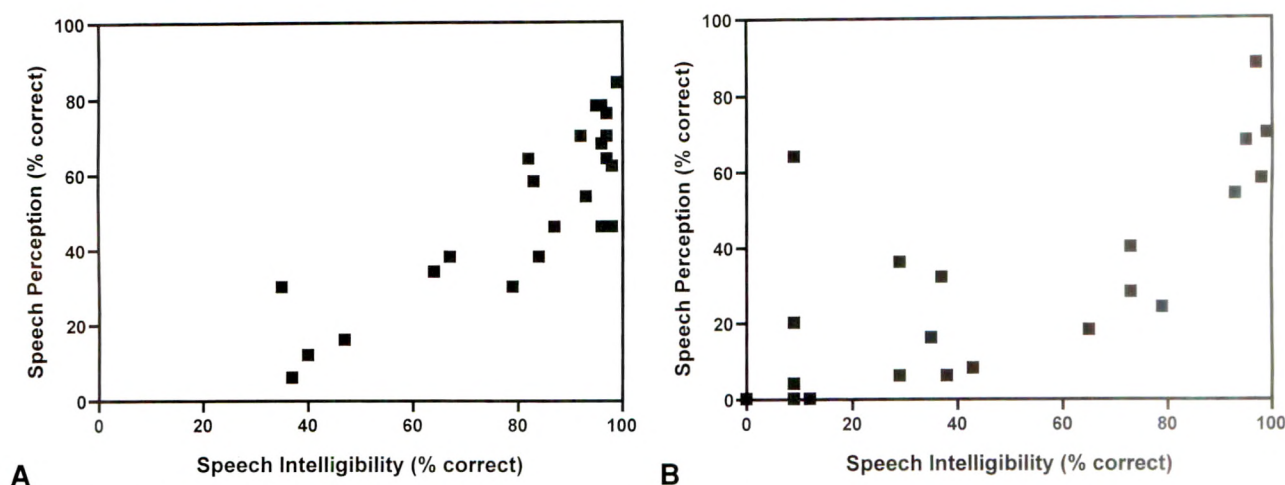
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INTRODUCTION

Poor speech intelligibility is commonly associated with children with profound hearing impairments; however, experience with multichannel cochlear implants appears to have a positive relationship with overall speech intelligibility. Generally speaking, the greater the experience with an implant, the higher the overall speech intelligi-

bility.¹ Speech intelligibility appears to be more accurate in children with cochlear implants who use auditory-oral communication as opposed to total communication.² Two limitations, however, are associated with these studies and other studies examining speech intelligibility in cochlear-implanted children. The first limitation is the relatively small number of subjects examined, and the second has



Overall speech perception and speech intelligibility scores, depicted for individual subjects in A) auditory-oral communication group and B) simultaneous communication group.

to do with the differing years of experience with an implant, which in most instances further reduces the number of subjects examined in longitudinal studies.

This study applied a cross-sectional design, holding implant device constant, in order to examine the relationship between open-set speech perception and overall speech intelligibility in children using either an auditory-oral or simultaneous (total) mode of communication. This study differs from previous studies in several ways. First, all subjects have a similar time frame of experience with a multichannel cochlear implant (range, 4 to 6 years). Second, the groups of subjects ($N = 23$ per group) are of similar chronological ages. Thus this study represents the first large set of data contrasting performance across a relatively large number of children with similar time frames of implant experience.

MATERIALS AND METHODS

The subjects were 46 eight- and nine-year-old children who had 4 to 6 years of experience with a Nucleus multichannel cochlear implant. Half of the children were involved in simultaneous modes of communication, and half were involved in auditory-oral modes. The communication mode used in the child's educational program was obtained from questionnaires completed by parents and therapists. Most of the children attended public schools (19 of the auditory-oral and 21 of the simultaneous communication children), and 6 children attended private schools (3 children in each group). The groups did not differ significantly in IQ, age at onset of deafness, duration of deafness, age at implantation, years of implant use, median family income, or median education of the father. Significant differences were observed in the mother's education (a mean of 4 and 2 years of college for the mothers of auditory-oral and simultaneous communication children, respectively) and the number of hours of therapy received during the 3 years after implantation. Auditory-oral children averaged 91, 96, and 88 hours of therapy for the first 3 years, and simultaneous communication children averaged 36, 49, and 58 hours of therapy.

Speech intelligibility was measured by recording 36 sen-

tences varying in length (3, 5, or 7 syllables) and contextual cues (low versus high contexts).³ Each child's productions were played to 3 normal-hearing judges, who were asked to write down the sentences. Total words understood were averaged across the 3 judges. It is important to note that the sentences used in this study are more difficult than those such as the Beginning Intelligibility Test (BIT) sentences.⁴ The difficulty is related to the fact that the sentences must be read, reflecting the older ages of our subjects relative to other speech intelligibility studies. Difficulty also is associated with the varying length of the sentences and the higher level of vocabulary in the sentences.

Open-set speech perception was measured with the Lexical Neighborhood Test (LNT),⁵ containing equal numbers of "easy" words (high-frequency words with few lexical neighbors) and "hard" words (low-frequency words with many neighbors).

RESULTS

Significantly higher open-set speech perception performance was observed for the children using auditory-oral communication as compared to the children using simultaneous communication on the LNT. Children using total or simultaneous communication achieved 30% correct (SD, 27%), whereas children using auditory-oral communication had 50% correct (SD, 22%). The difference in performance between the 2 groups was confirmed with statistical testing to be at the $p < .05$ level.

Similarly, the overall speech intelligibility scores were significantly higher for the children using auditory-oral communication than for the children using simultaneous communication. Speech intelligibility averaged 51% (SD, 36%) for the children using simultaneous communication and 81% (SD, 21%) for the children using an auditory-oral mode of communication. Analysis of variance revealed that the auditory-oral group was significantly more intelligible than the total communication group ($p < .01$).

The Figure, A, illustrates the individual performances of the auditory-oral communication group for speech per-

ception measured with the LNT and speech intelligibility measured with the McGarr sentences. A moderately strong relationship is evident between overall speech perception and intelligibility; that is, higher speech intelligibility appears in individuals who have higher speech perception scores.

The Figure, B, shows a similar depiction of speech perception and intelligibility scores for the children using simultaneous communication. Note the greater variation in performance of the group: some children have high speech intelligibility and speech perception scores, while other children have limited intelligibility and speech perception abilities. Also note that at least 1 child has very good speech perception scores with only limited speech intelligibility.

DISCUSSION

In this initial data set, the overall speech intelligibility appears to be better in children using an auditory-oral mode of communication than in children using simultaneous communication. The variability across subjects on speech intelligibility measures also appears to be greater in the simultaneous communication group of children. Positive relationships appear between speech perception and overall speech intelligibility in both groups of children. These data are in agreement with those of previous reports.^{2,4} Although these data are preliminary and further conclusions are warranted only after the larger pool of subjects (N = 180) is tested, the data suggest that overall speech intelligibility shares a moderately strong relationship with speech perception skills as measured by the LNT.

Parent-reported histories of communication mode do not explain the differences in performance noted across the 2 groups of subjects or the within-subject variation

noted within the groups. Preliminary examination does not indicate, at this time, a pattern of failure in using one mode of communication's leading to another mode of communication. That is, children using simultaneous communication were not necessarily children who had failed at auditory-oral communication. However, this issue must be carefully evaluated in the larger pool of subjects to be studied.

In addition, it is possible that the number of hours of therapy received by children after implantation also plays a significant role in the development of speech perception and intelligibility performance. The fact that children using an auditory-oral mode of communication underwent a greater amount of therapy suggests that the amount of therapy is an important consideration. Future studies with our larger pool of subjects will examine these factors more closely to determine how the number of therapy hours influences the performance of individual subjects, as well as the overall performance of the groups of subjects.

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ESTABLISHING NEW CRITERIA IN SELECTING CHILDREN FOR A COCHLEAR IMPLANT: PERFORMANCE OF "PLATINUM" HEARING AID USERS

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INTRODUCTION

An important criterion in determining candidacy for a cochlear implant is to demonstrate limited benefit with well-fitted hearing aids. Because performance with implants is steadily improving, the audiological criteria to determine candidacy are being reevaluated and expanded. As a consequence, performance by children with lesser severity of hearing loss would be important to document before new selection criteria are established. A number of significant advances have similarly occurred in the hearing aid industry with the emergence of digital-programmable technology and nonlinear processing schemes.

Thus, it would be reasonable to expect that performance with well-fitted hearing aids may improve for those children who exhibit sufficient residual hearing to benefit from such technological advances.^{1,2} The purpose of the present investigation was to document speech recognition performance in children with moderately severe-to-severe hearing loss by means of open-set tests presently administered to implanted children. The data should provide evidence to determine whether the criteria for implant candidacy should be modified to include those children who exhibit considerable open-set speech recognition with the use of hearing aids.

HA Groups 1 & 2

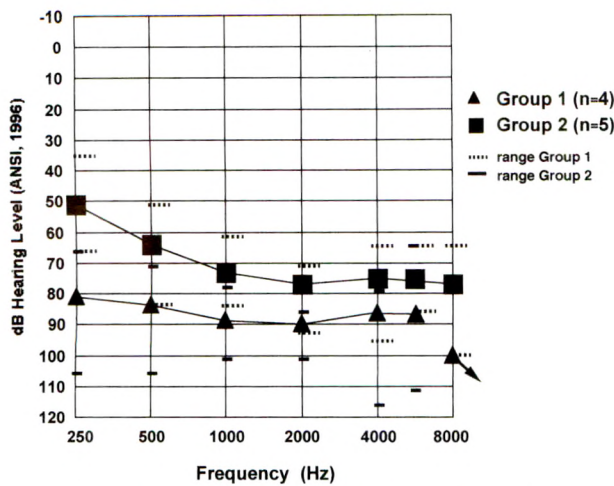


Fig 1. Mean unaided pure tone thresholds for children in hearing aid (HA) groups 1 and 2. Short solid lines represent range of thresholds for group 1, and short dashed lines represent range of thresholds for group 2.

METHODS

English-speaking children were recruited who had auditory thresholds between 60 and 100 dB hearing level (HL), aided Phonetically Balanced–Kindergarten (PBK) word list³ scores of 12% or better, and ages ranging from 5 to 10 years. Of those solicited, 9 children (5 girls and 4 boys) between the ages 5 years 9 months and 10 years 4 months (mean, 7 years 1 month) participated in the study. Eight of the children exhibited 3-frequency pure tone averages (PTAs) between 60 and 87 dB HL, and 1 child demonstrated a PTA of 98 dB HL, exhibiting thresholds in the severe range for frequencies above 2,000 Hz. All children were oral communicators; 5 were completely or partially mainstreamed and 3 were situated in auditory-oral private school settings. The average age at which hearing loss was identified was 2 years 7 months (range, 1 year 3 months to 5 years). Hearing aids had been worn for an average of 4 years 5 months (range, 2 years 6 months to 6 years). Eight of the children were fitted bilaterally with hearing aids; 1 child was given an implant in the poorer-hearing ear but was tested with only the hearing aid activated. The hearing aid fittings included linear peak

clipping, linear compression limiting, digitally programmable or completely digital instruments incorporating wide dynamic range compression.

Fifty words from list 3 of the PBK³ were presented by means of the recorded stimuli from the Auditec of St Louis compact disc. Newly recorded versions of the Lexical Neighborhood Test (LNT) and the Multisyllabic Lexical Neighborhood Test (MLNT)^{4,5} were administered, employing list 1 of the LNT (25 lexically easy words and 25 lexically hard words) and list 2 of the MLNT (12 lexically easy words and 12 lexically hard words). Four 10-sentence lists from the Hearing In Noise Test for Children (HINT-C)⁶ were administered; lists 3 and 4 were presented in quiet, and lists 6 and 12 were presented in noise (shaped to the long-term average speech spectrum of the original HINT sentences⁷). The noise was delivered 5 dB below the speech, a level shown to produce scores in the middle range of the performance-intensity function for listeners with this magnitude of hearing loss.⁸ Familiarization with each test and talker was initiated before formal testing, by application of stimuli from lists not used in the study. The speech recognition tests were administered in the sound field at a 0 degree azimuth with the hearing aid(s) activated at the “use” setting. Stored as digital files, the stimuli were routed to an audiometer for amplification and delivered to the listener by way of a loudspeaker at 65 dB SPL. Before experimental testing, electroacoustic measurements were performed on the hearing aids to verify that the instruments were operating properly. Real ear probe tube microphone measurements were conducted to ensure that the aided responses were audible and did not exceed the predicted loudness discomfort level in reference to targets specified by the Desired Sensation Level hearing aid fitting algorithm.⁹

RESULTS

Performance on the PBK yielded a mean word score of 56% (SD, 24.9%) and a phoneme score of 74% (SD, 25.8%). Because the data formed a bimodal distribution, the word and phoneme scores of individual children were divided into 2 performance groups. Hearing aid (HA) groups 1 and 2 were differentiated statistically by PTA on the Mann-Whitney U test ($U = 1$, $p < .05$), but not by age at time of testing, duration of hearing aid use, or hearing

PBK Word Score

PBK Phoneme Score

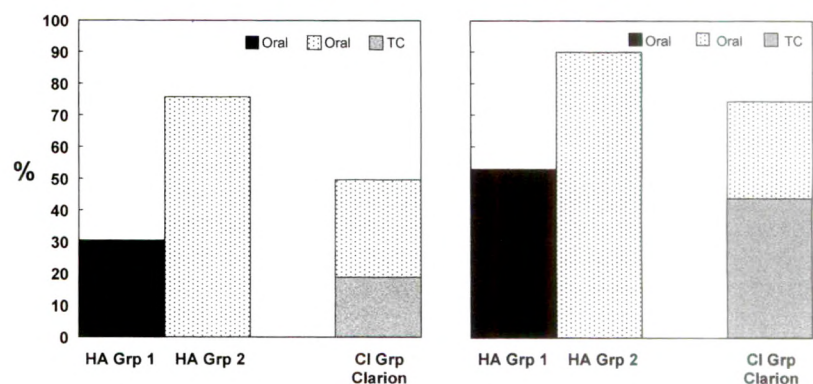


Fig 2. Mean PBK (Phonetically Balanced Word Lists–Kindergarten) word and phoneme scores for HA groups 1 and 2 and group of children using Clarion multichannel cochlear implant (CI). Implant data are segmented according to communication mode: oral communication and total communication (TC).

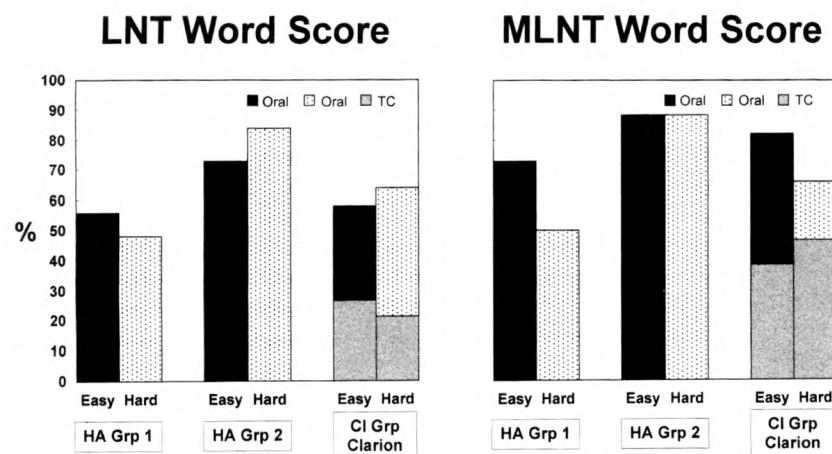


Fig 3. Mean LNT (Lexical Neighborhood Test) and MLNT (Multisyllabic LNT) lexically easy and hard word scores for HA groups 1 and 2 and group of children using Clarion multichannel cochlear implant. Implant data are segmented according to communication mode: oral and TC.

aid type. Audiograms for each group are displayed in Fig 1. Group 1 included 4 children with PTA hearing losses in the better hearing ear that ranged from 82 to 98 dB HL and had a mean of 88 dB HL. Group 2 included 5 children with a mean PTA loss of 71.4 dB HL, ranging from 60 to 82 dB HL. For both PBK word and phoneme analyses, group 2 obtained significantly higher scores than group 1 ($U = 0$, $p < .05$).

Placing these results in perspective, Fig 2 compares the HA group data with live-voice performance scores from a group of implant-fitted children (CI group) provided by Advanced Bionics Corporation; all children were Clarion multichannel users of the Continuous Interleaved Sampler (CIS) strategy (monopolar stimulation mode). These data represented the 2-year postimplant test interval for 12 to 14 children given implants between the ages of 2 years 8 months and 15 years 1 month. The implant data were segmented according to communication mode (oral communication and total communication). For PBK words and phonemes, the results in Fig 2 show that the implanted children who communicated orally yielded higher mean

scores than HA group 1, but lower mean scores than HA group 2. The implanted children who used total communication exhibited lower mean scores than HA group 1.

The mean LNT word scores were 65% (SD, 15.9%) for lexically easy words and 68% (SD, 20.3%) for lexically hard words. The mean MLNT word scores were 82% (SD, 19.8%) for easy words and 71% (SD, 24.2%) for hard words. The percent correct scores were arc sine-transformed and subjected to a repeated-measures ANOVA to test the main effects of test measure (LNT versus MLNT) and lexical difficulty (easy versus hard) for the sample of 9 children. Only test measure reached statistical significance ($F(1,8) = 8.804$, $p < .05$); the MLNT scores were significantly higher than the LNT scores. The Mann-Whitney U test was conducted on the raw scores to compare HA groups 1 and 2 on the LNT and MLNT measures. The groups were found to be differentiated only by the lexically hard LNT ($U = 0$, $p < .05$), and MLNT words ($U = 0.5$, $p < .05$). The group data for recorded stimuli also were compared with implant performance for live-voice stimuli, displayed in Fig 3. Again, it will be seen that HA group 2 had higher mean scores than the 2 implanted groups, but HA group 1 demonstrated lower mean scores than the orally communicating implant group.

HINT-C (Quiet) Word Score

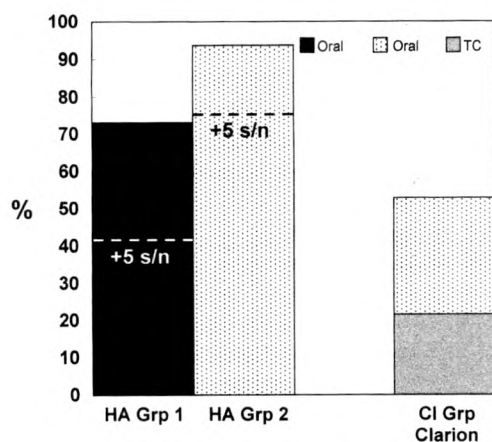


Fig 4. Mean word scores for HINT-C (Hearing In Noise Test for Children) sentences in quiet for HA groups 1 and 2 and group of children using Clarion multichannel cochlear implant. Implant data are segmented according to communication mode: oral and TC. Dashed line represents mean word scores in noise for 2 hearing aid groups.

The mean HINT-C sentence scores for the sample of 9 children were 58% (SD, 27.7%) in quiet and 28% (SD, 20.9%) in noise. When scored by words correct, the mean scores increased to 85% (SD, 17.7%) in quiet and 61% (SD, 31%) in noise. The sentence and word scores obtained both in quiet and noise were analyzed to compare HA groups 1 and 2. The groups were differentiated statistically only on testing in quiet both for the sentence score ($U = 1$, $p < .05$) and word score ($U = 2$, $p < .05$). Figure 4 compares the mean word scores in quiet for the 2 HA groups and the CI group, for whom testing was conducted with taped stimuli. For informational purposes, the mean scores in noise are presented as a dashed line for the HA groups. When tested in quiet, HA groups 1 and 2 both demonstrated higher mean scores in comparison to the scores produced by the implanted children. Of note, 1 child who used digital hearing aids in HA group 1 (exhibiting a PTA of 85 dB HL) produced scores higher than most of the children in HA group 2 in the noise condition.

CONCLUSIONS

In summary, performance data from 9 children with hearing loss ranging between 60 and 98 dB HL formed 2 distributions based on the 3-frequency PTA: 60 to 82 dB HL and 82 to 98 dB HL. Among the tests administered, the PBK word lists, the lexically hard LNT and MLNT words, and the HINT-C sentences presented in quiet were found to be sensitive measures in differentiating between-group performance. The children in the better hearing group (60 to 82 dB HL) produced higher mean scores on all measures when compared to a group of implanted children. The children in the poorer hearing group (82 to 98 dB HL) yielded either similar or better mean scores than the group of implanted children who used total communication; the children in this group demonstrated lower mean scores on most measures when compared to orally communicating implanted children.

These results would suggest that children with 24 months of cochlear implant use have the potential to perform similarly to and, in some cases, even better than children who exhibit losses in the severe range of hearing (80 dB HL or poorer). Such findings lend some support to implanting "select" patients who exhibit more residual hearing than do children who would typically be considered. When considering such children for a cochlear implant, one should conduct preimplant testing with taped stimuli and, in some cases, in the presence of background noise. Similar testing should be conducted with high-performing implanted children to provide the data required in making these comparisons. The option of fitting new signal processing hearing aids should not be ruled out when a child with aided residual hearing is being considered for a cochlear implant. As was noted, at least 1 child with a PTA of 85 dB HL and fitted with digital hearing aids performed comparably to children in the better hearing group, particularly

when tested in the presence of background noise. It is our hope that these data will provide useful information to clinicians who may be confronted with children who exhibit severe hearing loss but are not performing as well as might be expected from their present amplification devices.

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LONG-TERM RESULTS OF COCHLEAR IMPLANTS IN CHILDREN WITH RESIDUAL HEARING

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The success of cochlear implants in children has created an intriguing clinical dilemma for cochlear implant teams. Children with implants are frequently developing better speech and language skills compared to severely hearing-impaired classmates who use hearing aids.¹⁻⁴ This has prompted parents of severely hearing-impaired children to inquire whether a cochlear implant would provide more benefit than a hearing aid. These questions have stimulated some of us to consider expanding implant audiological selection criteria. Unfortunately, published children's implant performance data cannot be used as a comparative benchmark, since the results were obtained in

children who had no preoperative speech perception, as candidate selection was limited to such children. Intuitively, one would expect that individuals with more preoperative hearing would have better speech perception scores with an implant, because they would be expected to have more intact auditory systems. However, caution must be exercised, because it would be undesirable to put an implant in a child who would perform better with a hearing aid. Recently, the Iowa implant team has demonstrated that speech understanding performance with an implant in postlingually deafened adults is dependent upon the duration of deafness and preoperative speech percep-

TABLE 1. TWO-YEAR FOLLOW-UP GROUP

Subject	Age (y)	Preop PTA (dB)		Binaural PBK Word (%)	
		Right	Left	Preop	2 y
IA1	11	108	110*	12	80
IA2	6	100*	93	24	70
IA3	7	93	106*	48	74
NY1	6	95	120*	4	64
NY2	4	120	122*	20	72
IN1	5	103	105*	8	80
IN2	6	97	98*	4	84

PTA — pure tone average, PBK — Phonetically Balanced-Kindergarten test.

*Implanted ear.

tion measures.⁵ Surprisingly, another obstacle to arriving at an informed decision about implant selection criteria is the lack of open-set speech perception data from large series of severely hearing-impaired children who use hearing aids. A recent study by Eisenberg et al (this supplement, pp 30-33) examining speech perception test results from a small group of severely hearing-impaired children may provide some guidance.

In 1996, we reported our collective preliminary experience providing cochlear implants to 6 children who had some residual hearing.⁶ This group of children would be characterized as "gold hearing aid users" or better, because they demonstrated preoperative Phonetically Balanced-Kindergarten (PBK) word scores ranging between 4% and 48% in a binaural aided condition. With a cochlear implant, they exhibited rapid growth in open-set speech perception skills during the first 6 months of implant use.

In this report, we will review the speech perception skills of these children after 2 years of implant usage and will provide preliminary word scores on 8 children recently fitted with implants. In addition, we will suggest, on the basis of these results, expanding the audiological selection criteria that should be considered for future controlled clinical trials of cochlear implants.

METHODS

Children were determined to be appropriate candidates for a cochlear implant on the basis of selection criteria developed at each center employing methods and measures used since 1987, when the pediatric multichannel implant clinical trials began.⁷⁻⁹ All centers administered

TABLE 2. SIX-MONTH FOLLOW-UP GROUP

Subject	Age (y)	Preop PTA (dB)		Binaural PBK Word (%)	
		Right	Left	Preop	6 mo
IA4	11	97*	93	12	48
NY3	12	103*	98	22	40
NY4	6	107	118*	10	68
NY5	9	105	107*	20	14
NY6	4	103*	98	16	76
NY7	11	107	108*	24	68

*Implanted ear.

TABLE 3. RESULTS

	Mean	Range
PTA, implant ears (dB)	108	98-120
PBK words, binaural aids (%)		
2-y group	17	4-48
6-mo group	17	10-24
PBK words, implant only (%)		
2-y group	75 ± 6.4	64-84
6-mo group	52 ± 23	14-76

the open-set PBK word lists scored for word recognition and phoneme recognition.¹⁰ The test material was presented in the form of recorded stimuli in a sound field at a comfortable listening level. All 3 institutions performed the tests similarly. Pure tone averages (PTAs) were obtained for each ear at 500 Hz, 1 kHz, and 2 kHz. All children were in an aural education environment. Cochlear implantation was always performed in the poorer hearing ear. A Nucleus 22 implant was used in 8 children, 3 received a Nucleus CI24M, and a Clarion device was placed in 2 children. Seven children have been using their cochlear implant for over 2 years, while the other 6 have 6-month results only. Results for the group with 2 years of experience and the group with 6 months of experience are reported separately.

RESULTS

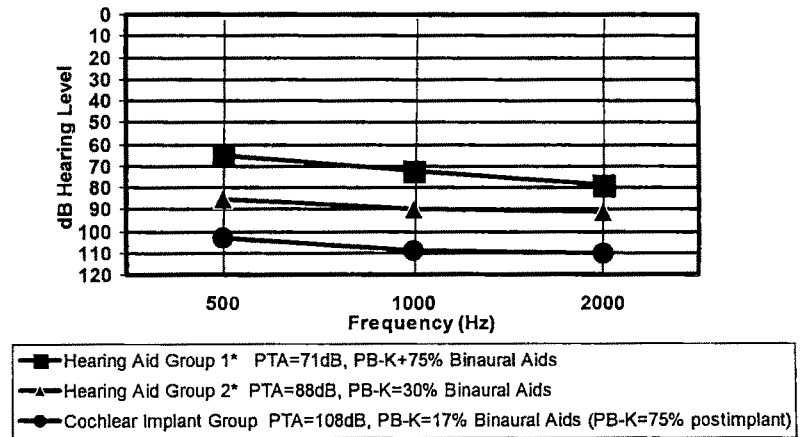
The age at implantation, PTA of each ear, preoperative PBK word score in the binaural aided condition, and 2-year postimplant PBK word score results are shown in Table 1. The ear selected for implantation was the poorer hearing ear as indicated by the PTA and preoperative PBK word scores. The age at implantation in this group was between 4 and 11 years. The PTA for the implanted ears ranged between 98 and 120 dB hearing level (HL), with a mean of 108 dB HL. The preoperative PBK word score with hearing aids ranged between 4% and 48%, with a mean of 17%. The child with a 48% preoperative PBK word score had 0% discrimination in the implanted ear. He was unable to use a telephone and wanted to proceed with implantation. After 2 years of experience with a cochlear implant, the PBK word understanding scores ranged between 64% and 84%, with a mean of 75% ± 6.4%.

A second group of children with similar preoperative hearing have been fitted with implants, but only 6-month follow-up data have been collected. Their age, PTA, preoperative binaural aided scores, and 6-month PBK word scores are shown in Table 2. It is remarkable that 3 children are demonstrating 68% to 76% word understanding at 6 months. One subject is doing worse than before surgery on the PBK word test, but other tests, such as the Lexical Neighborhood Test (LNT) and Hearing In Noise Test (HINT) sentence scores, are much improved for this child. The results for both the 2-year and 6-month groups are summarized in Table 3.

DISCUSSION

Cochlear implants have been of great benefit for the majority of bilaterally profoundly deaf children who have

Auditory thresholds and speech perception of children using hearing aids. Data marked in key with asterisk are from Eisenberg et al, this supplement, pp 30-33.



received them. Speech perception, speech production, and language skills have improved over time after implantation. These results have prompted the Iowa, New York, and Indiana implant centers to investigate the use of cochlear implants in a select group of children who receive benefit from hearing aids but do not develop sufficient hearing to achieve normal speech perception and production levels for their age.

The speech perception skills of this group of children 2 years after implantation are extremely encouraging. The mean score of 75% on the PBK word test is similar to that of a small group of children who have a 71-dB PTA, are moderately hearing-impaired, and are hearing aid users. A more severely hearing-impaired group of hearing aid users (88 dB PTA) could only achieve 30% word understanding on the PBK test (see Figure and see Eisenberg et al, this supplement, pp 30-33). Our children had a 108-dB PTA in the implanted ear before implantation. The PBK speech perception scores of this group are quite different from the usual results achieved by prelingually profoundly deaf children without preoperative word understanding. A group of 20 prelingually deaf children followed by the Iowa cochlear implant center had a mean PBK word score of 20% at 6 years.¹¹ The children given implants between 2 and 4 years of age had much better results (PBK word score mean, 40%, N = 7) than those given implants between 5 and 8 years of age (PBK word score mean, 16%, N = 12). In the present study, age at implantation does not appear to have an effect on performance in children with residual hearing; the children given implants at ages 11 years (subject IA1) and 4 years (subject NY2) exhibited similar word scores. There may be several reasons for this finding, including the size of the sample, the narrow range of distribution of preoperative word scores, and the fact that the preoperative PBK score was obtained in the binaural aided condition and was not specific for the implanted ear.

It is suspected that limited preoperative speech perception scores reflect a more intact auditory system, including inner hair cells, dendrites, ganglion cells, and central pathways, compared with that in profoundly deaf subjects without speech perception. Individuals with more intact auditory systems should be able to more accurately process speech signals presented by multichannel cochlear

implants. The duration of deafness has been the most sensitive predictor of auditory performance with an implant. Recently the Iowa implant team demonstrated a significant relationship between residual auditory function (preoperative Central Institute for the Deaf [CID] sentence scores) and postoperative consonant-nucleus-consonant word understanding performance. In our postlingually deafened adult patients, the duration of deafness and the preoperative CID sentence score accounted for more than 70% of the variance in 40 subjects.⁵

In summary, this selected sample of children with residual hearing and limited word understanding with hearing aids achieved significantly greater open-set word recognition with a multichannel cochlear implant than did profoundly deaf children with no preoperative word recognition. The poorest result with an implant in this population was 64% on the PBK word test after 2 years of experience with an implant. This group of profoundly hearing-impaired children with residual hearing exhibited speech perception scores similar to those of a group of moderately hearing-impaired children (71 dB PTA) using hearing aids. It would seem reasonable to study a larger cohort of children with preoperative PBK word scores up to 40% in the binaural aided condition. Children who participate in this study should be at least 5 years of age so that the speech perception test materials are appropriate for their level of language development. Finally, implantation should be limited to the poorer ear for this study.

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BORDERLINE PEDIATRIC COCHLEAR IMPLANT CANDIDATES: PREOPERATIVE AND POSTOPERATIVE RESULTS

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INTRODUCTION

Research has demonstrated that cochlear implants may provide significant benefit to profoundly deaf children.¹⁻³ The recommended criteria for determining pediatric cochlear implant candidacy have traditionally included hearing impairment of 90 dB hearing level (HL) or poorer across the speech frequencies and no better than chance performance (0%) on open-set word and sentence materials.⁴ Early expectations held that a child meeting these criteria could be expected to perform similarly to a child with a severe hearing impairment after implantation.⁵ Cochlear implant centers evaluate many children whose unaided hearing levels place them in the range of profoundly hearing impaired, but whose aided speech perception exceeds chance performance on open-set testing and who score extremely high on closed-set measures. In general, these children are involved in good oral or auditory-verbal rehabilitation programs and have learned through exhaustive work to use every auditory cue available. Though they score higher than other children with similar hearing loss in a quiet test environment, they may in fact be struggling to communicate in stressful listening environments such as school, church, or home.

The University of Miami Ear Institute (UMEI) cochlear implant program has implanted over 100 children. Established in 1990, our initial criteria did not deviate from the guidelines recommended by the US Food and Drug Administration. However, as we began to evaluate children with more apparent auditory capabilities, particularly those in strong auditory-based therapy programs, we began to reassess the candidacy criteria and to look at the individual child's ability to effectively hear and understand in less-than-ideal listening conditions. We have also accrued a growing population of children with cochlear implants whose performance exceeds that of children excluded from candidacy on the basis of speech perception test scores. Performance of these implanted children suggests that the implant may offer other listening advantages that allow the user to communicate more effectively than profoundly hearing-impaired children who demonstrate very limited

speech understanding in quiet with hearing aids. The concept of performing implantation in children with greater degrees of speech perception abilities is not without precedent. Yaremko and Gibson⁶ discussed children who were "good" hearing aid users and obtained scores between 30% and 50% on open-set tests, stating that these scores in fact may be markers for potential performance with the cochlear implant. Similarly, Cowan et al⁷ reviewed results from pediatric patients with various degrees of residual hearing and various preoperative open-set scores. Their data demonstrated that more than 90% of children with residual hearing measured at 70 dB HL through 2,000 Hz had no preoperative open-set understanding, yet achieved postoperative open-set word understanding of 20% to 50%. Such results suggest that consideration should be given to children with more residual hearing and minimal speech understanding.

METHODS

Subjects were selected from a pool of 102 children given implants at the UMEI between 1991 and 1998. To qualify for inclusion, a child had to have exceeded recommended selection criteria by exhibiting 1 or more of the following: unaided pure tone average (PTA) of less than 90 dB HL; aided PTA of 35 dB HL or better; speech awareness threshold (SAT) of 35 dB HL or better; and open-set word or sentence scores better than chance. In addition, subjects needed a minimum of 3 months of experience with the cochlear implant.

A review of records maintained by the UMEI program was undertaken to identify children meeting the inclusion criteria for this study. The preoperative and most recent postoperative audiometric and speech perception data were recorded for each of the children meeting the inclusion criteria. The open-set speech perception measures included the Phonetically Balanced-Kindergarten (PBK) word lists and the Glendonald Auditory Screening Procedure or Common Phrases Sentences. The results were analyzed for significance of preoperative and postoperative differences in performance by ANOVA.

TEST RESULTS

Subject	Age at Onset (y)	Age at Surgery (y)	Length of CI Use (mo)	Comm Method	PTA (dB)			SAT (dB)		SRT (dB)		PBK (%)		Sentence (%)	
					Preop			Preop		Preop		Preop		Preop	
					Unaided	Aided	CI	Preop	CI	Preop	CI	Preop	CI	Preop	CI
S1	9	11	6	Oral	97	37	33	35	15	40	25	12	64	20	91
S2	0	5, 6	18	Oral	98	40	27	30	20	CNE	35	0	80	10	68
S3	0	1.3	12	Oral	92	42	15	25	---	CNE	25	0	100	0	100
S4	0	5	24	Oral	92	42	27	30	25	45	25	2	68	30	90
S5	0	11	12	Oral	100	28	33	10	---	25	35	0	44	0	90
S6	0	8	12	Oral	108	43	33	25	25	CNE	45	4	14	0	94
S7	4	5	48	Oral	89	45	17	30	10	CNE	20	12	88	0	100
S8	9	9	36	TC	82	50	30	30	25	CNE	30	2	64	30	100
S9	0	7	24	Oral	103	30	25	30	20	CNE	35	0	98	10	100
S10	0	14	24	Oral	100	52	28	30	30	CNE	40	0	28	10	100
S11	0	10	15	Oral	103	37	32	35	---	CNE	30	16	40	0	94
S12	0	9	48	Oral	93	45	30	30	25	CNE	35	0	38	0	74
S13	0.8	12	3	Oral	97	47	32	35	20	50	45	0	72	36	97
Mean	1.8	8.3	22		96	41	28	29	22	40	33	4	61	12	92

CI — cochlear implant, Comm — communication, PTA — pure tone average, SAT — speech awareness threshold, SRT — speech reception threshold, PBK — Phonetically Balanced-Kindergarten test, CNE — could not elicit, TC — total communication.

All children were evaluated before and after implantation at the UMEI. Audiometric testing at the UMEI is routinely completed in an American National Standards Institute-approved and -calibrated sound suite. Preoperative aided testing of pediatric cochlear implant candidates is performed monaurally and binaurally to determine the best aided condition. Speech perception testing is administered in the child's best aided condition by means of live-voice presentation of materials. A black mesh screen is used to cover the examiner's face and eliminate visual cues. Postoperative procedures are performed in an identical fashion in only the cochlear implant condition.

RESULTS

A review of records revealed that 13 children given implants at the UMEI met inclusion criteria for this study. The decision to perform implantation in these children was based on close interaction between the implant center, the child's family, and the child's primary service provider. Extensive counseling regarding expectations was provided to the families. Twelve children received oral or auditory-verbal — and 1 child total communication — habilitative services. All subjects were believed to be hearing-impaired at birth; however, 2 were known to have progressed to profound hearing loss postlinguistically, 2 perilinguistically. All children were from native English-speaking homes.

The subjects ranged in age from 5 to 14 years, with a mean age of 8 years 3 months at the time of implantation. The mean age at identification for the group was 1.9 years. The mean length of hearing aid use was 7 years 1 month. The mean preimplant PTA was 96 dB HL unaided and 41 dB HL aided. The mean aided SAT was 29 dB HL. The mean preoperative word identification score was 4%, and the sentence identification score was 12%.

Implant experience ranged from 3 to 48 months, with a mean length of implant use of 22 months. Two children used Clarion cochlear implants, 2 used Nucleus CI24M cochlear implants, and 9 used Nucleus CI22 cochlear im-

plants. The mean cochlear implant PTA was 28 dB HL, and the mean cochlear implant SAT was 22 dB HL. The mean word identification score was 61%, and the mean open-set sentence score was 92%.

Paired *t*-tests showed that the PTA, word recognition, and sentence recognition differences between the preoperative and postoperative results were all statistically significant ($p < .0001$). The Table gives preoperative and postoperative test results. Before implantation, few children displayed a speech recognition threshold, whereas after implantation all were able to do so.

DISCUSSION

The results of this study revealed that all of the 13 borderline pediatric candidates implanted at UMEI received significant benefit from the cochlear implant compared with that received from hearing aids. These data support the findings of Cowan et al⁷ suggesting that patients with more residual hearing have more potential for success with the cochlear implant. However, in considering application of expanded criteria to children younger than 2 years, caution should be used. The only child younger than 2 years included in this study had experienced ideal circumstances for implant candidacy: identification and aiding at 3 months, consistent auditory-verbal therapy, and exceptional family support.

These results were also compared with those of the "gold hearing aid users" as reported by Miyamoto et al.³ The mean open-set sentence understanding was reported to be approximately 48% for the gold hearing aid users, with a range of approximately 0% to 85%, compared with a mean of 92% and a range of 68% to 100% for our group of implant users. Insufficient data are provided in that study for a detailed comparison of results.

The results reported here strongly support the expansion of candidacy criteria established in the Nucleus CI 24M pediatric clinical trials. The technology of today's cochlear implant devices allows for greater development

of speech and language by providing information that was simply not available in early-generation devices. The cochlear implant community should not only strongly consider expanding device availability to children with more residual hearing but should strive to raise expectations for children with implants to reflect the improved capabilities of multichannel devices.

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SPEECH PERCEPTION OUTCOME MEASURES IN PRELINGUALLY DEAF CHILDREN UP TO FOUR YEARS AFTER COCHLEAR IMPLANTATION

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INTRODUCTION

The aim of our study is to evaluate the auditory performance of congenitally deaf children having cochlear implants, with a range of speech perception tests administered during a 4-year follow-up period. In common with other groups,¹⁻³ we are particularly interested in how the age at implantation affects outcome. One of the difficulties with this task is that in addition to the time of implantation, several factors influence performance, such as age at onset of deafness,³ residual hearing, educational setting, family support, and communication mode.^{4,5} Ideally, one would need to study a homogeneous population in which all of these factors are equal; this is, of course, impossible. However, our own group of patients is probably more homogeneous than most others. In part, this is because Canadian health care resources for cochlear implantation have been limited, and therefore, our eligibility criteria for implantation have been relatively strict. Stringent audiometric inclusion-exclusion parameters were adhered to. We have only performed implantation in children with nonossified and patent cochleas allowing full electrode array insertion. All patients' families were committed to oralism as the main communication mode for their children. We have also had a rigid policy of not implanting children unless auditory-verbal therapy was planned in either educational or health care environments. Our own program is heavily weighted toward providing auditory-verbal therapy, either within the program or in liaison with programs in the community. Our data are based only on speech perception tasks that were evaluated in our own institution under consistent testing conditions.

We report here results from 66 children given implants since 1989⁶ and tested annually with a range of speech perception tests. The data presented here are the results

of PBK, TAC, and WIPI tests (see Methods). Our focus is on the progression of patients implanted at a younger age compared with that of patients provided with implants when older. Our data provide clear evidence that patients fitted with implants at a young age progress substantially better than those given implants later.

MATERIALS AND METHODS

Our subject group consisted of 66 children (35 girls, 31 boys). All patients were congenitally deaf, ie, with pure tone averages in the better ear ranging from 95 to 120 dB hearing level. The range of age at implantation was 1.9 to 15.4 years (mean age at implantation, 6.0 years), and the mean time since implantation was 39 months. In the data presented in Figs 1-3, the number of subjects tested is explicitly noted. All children received the Nucleus Mini 22-Channel cochlear implant system (Cochlear Corporation) with full insertion of the electrodes. There were minimal complications.⁷

Several speech perception tests were used to assess the children before and after implantation. In this study we report on the results at 0, 1, 2, 3, and 4 years after implantation on the WIPI, TAC, and PBK tests. The tests are briefly as follows: the WIPI (Word Intelligibility by Picture Identification) is a closed-set test, utilizing a 6-choice picture format. The score by chance is 16%. It is one of the most widely used closed-set tests. The PBK (Phonetically Balanced-Kindergarten) word test is an open-set test. It consists of 4 lists of 50 words, 1 list representing 1 complete test. Half of the list can be administered, as is done especially with younger children. In this case, each correct word recognition is 4%. The score by chance is 0. The TAC (Test of Auditory Comprehension) is used to assess different areas of auditory comprehension. This test is divided into 10 subtests. Levels 1 through 3 assess su-

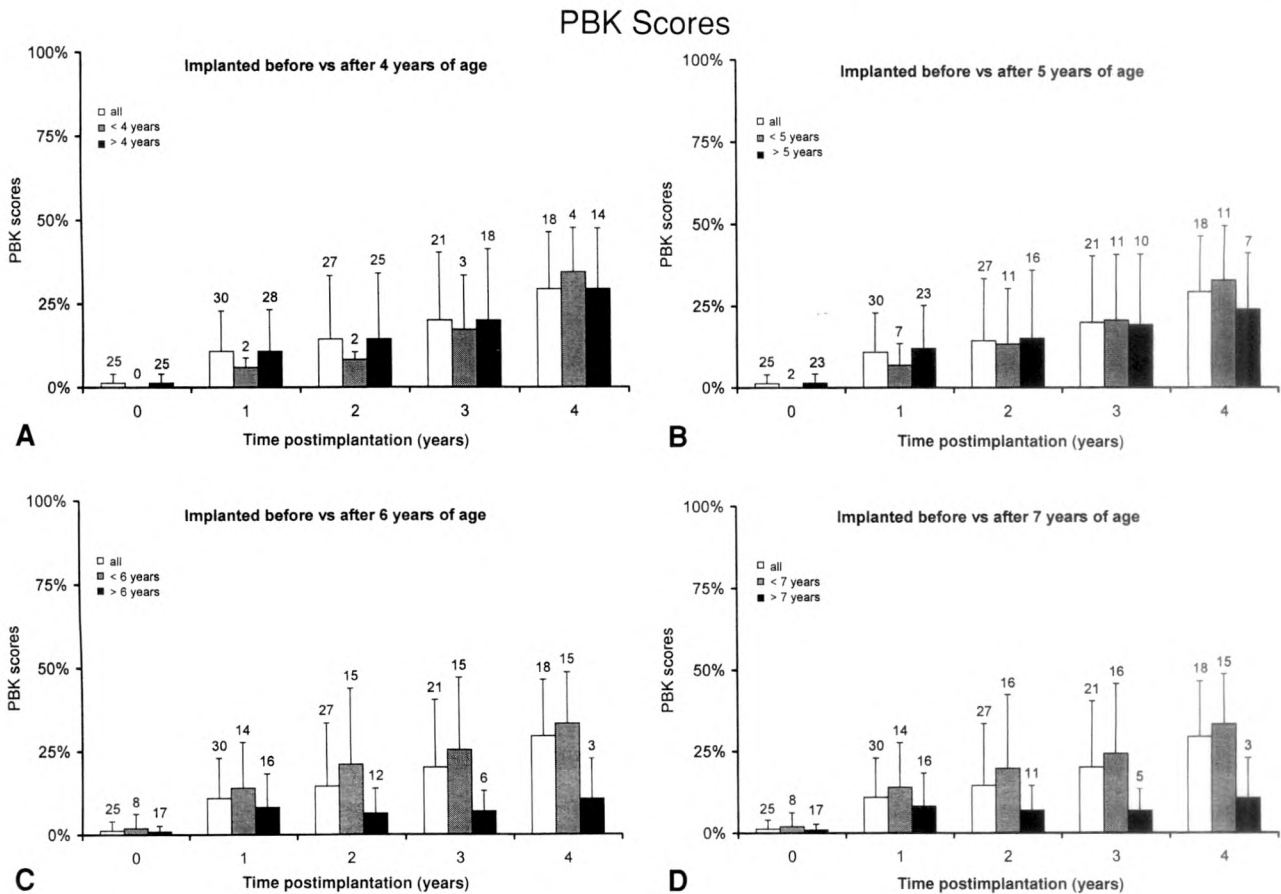


Fig 1. Results of PBK (Phonetically Balanced–Kindergarten) tests (percent correct scores) for 66 subjects assessed before (0 year) and at yearly intervals after cochlear implantation. Average scores and 1 standard deviation are shown. Scores from all subjects are shown by white bars. Data are divided into 2 groups according to age at implantation: 4 years (panel A), 5 years (panel B), etc. Results from children given implants at younger ages are shown by gray bars, those of older children by black bars. Numbers of subjects in each test group are indicated.

prasegmental discrimination — for example, differentiation between speech and nonspeech stimuli. The higher subtests involve vocabulary and comprehension abilities and are more dependent on cognitive skills, language, and memory. The highest level passed by the child is recorded as his or her score. We chose these 3 tests from a battery of many evaluation methods because they appear to monitor the essential features of auditory function.

RESULTS

Figure 1 shows PBK test results obtained before implantation (labeled 0) and 1, 2, 3, and 4 years after implantation. For each of these 4 graphs, our subjects are divided into 2 groups according to their age at the time of implantation. Thus panel A compares children fitted with implants before and after age 4. The white bar represents the data for all the children together and is therefore the same in all panels. The gray bar shows the average score for the children given implants when they were younger than 4 years, and the black bar shows the results of the subjects given implants when they were older than 4 years. The other graphs are presented in the same way, comparing performance of children given implants before and after 5 years (B), 6 years (C), and 7 years (D). In each Figure, the number of subjects is indicated and the variance in the data is also shown.

Taken together, we can see a general increase in performance on the PBK test over the 4-year period after implantation. On average, as the white bars indicate, subjects reach a level of approximately 30% open-set recognition after 4 years, although there is considerable variation from one subject to another, as indicated. When the subjects are divided into 2 groups according to their age at the time of implantation, considerable differences in the progression of performance are revealed when that division is before and after 6 years. Thus, as seen in Fig 1C, there is a relatively large change in the growth of PBK scores between subjects given implants before age 6 (gray bar) compared with after 6 (black bar). At 4 years after implantation, in the group given implants when younger than 6 years, the average score was 33%, with a range between 12% and 72%. The average value for the children given implants after age 6 was 11%.

Figure 2 reports the WIPI test results obtained before implantation and 1, 2, 3, and 4 years after implantation, with the same display of data as in Fig 1. The average score for all the patients before implantation was 23%, and there was approximately a 10% increase in the scores each year after implantation in both groups, with an average score of 56% at 4 years after implantation. As the gray bars in Fig 2A,B indicate, patients given implants at a younger age have an average score that is lower at the

WIPI Scores

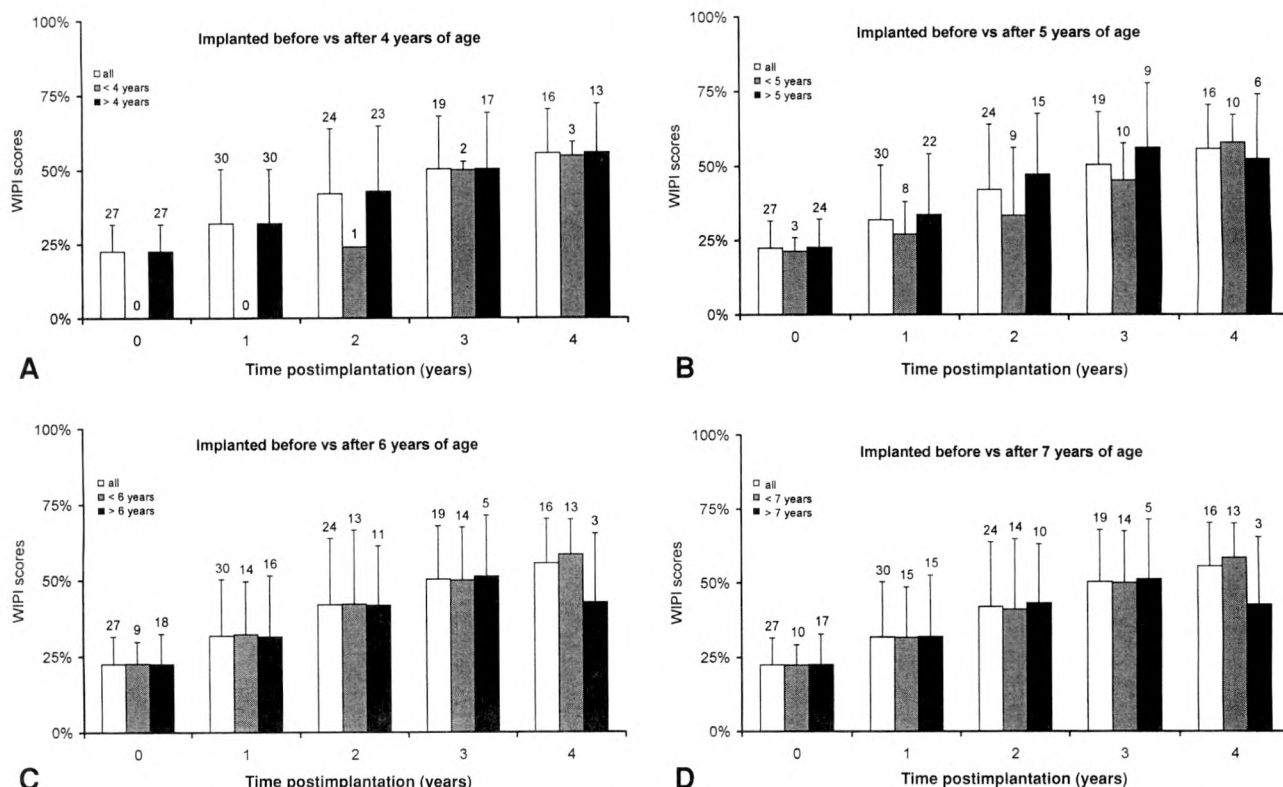


Fig 2. WIPI (Word Intelligibility by Picture Identification) test results (percent correct scores) for children fitted with implants before and up to 4 years after implantation. Data format is same as in Fig 1.

beginning, but it tends to reach the same value or even a higher value than that of the older implant recipients at 4 years after implantation. When subjects are divided at implant ages of 6 and 7 years (panels C and D), there is no obvious difference in terms of average score between the younger and the older implantees.

Figure 3 shows the TAC test results obtained before implantation and 1, 2, 3, and 4 years after implantation, in the same fashion as the data of the other Figures. The average for all the children was 0.7 before implantation (white bar) and 5.7 after 4 years. As shown in each of these graphs, before implantation the younger subjects (gray bars) attained a lower average level of speech perception skill than the older ones (black bars). However, in general, those younger subjects eventually reach or exceed the level of the older ones.

DISCUSSION

The results of all the tests used in this study suggest that greater benefit may be obtained from implanting prelingually deaf children at the earliest possible age. These results confirm what has been previously reported¹⁻³ and are in line with a commonly accepted notion of an age-dependent plasticity of neurosensory development. The results on the PBK tests, in particular, show most clearly the difference in performance of children implanted at a younger age compared with those implanted later. This is distinctly seen in the lower panels of Fig 1, showing the difference in performance of children implanted before 6

or 7 years of age (left and right graphs, respectively; gray bars) compared with those implanted after 6 or 7 years of age (black bars). The results of the WIPI test and the TAC do not show such large differences between the groups, a finding that has been reported by others.¹ This may be due to the more difficult nature of the PBK test, which involves "open-set" tasks.

Perhaps the most informative aspect of these data is not so much in the absolute values, but in the progression of performance over time. With the PBK test (Fig 1), the younger-implanted subjects were able to improve their scores over time, showing no evidence of a plateau in performance. In contrast, the average performance in the subjects given implants at later ages showed very little improvement over time. Thus, it appears that on average, the children implanted after age 6 to 7 make little progress in open-set tests. This observation is similar to that often found in prelingually deaf implanted adults.^{2,8}

Subsequent to cochlear implants' being approved for use in children, there has been some discussion on the issue of whether congenitally deaf children would benefit from implants. This has been more an issue in health care systems in which there is a limitation in resources for cochlear implants and thus where the provision of an implant tends to be made only for those in whom a significant improvement in oral communication is likely. The question has been asked as to whether there is an age of implantation above which performance with a cochlear implant significantly decreases. Others have posed the

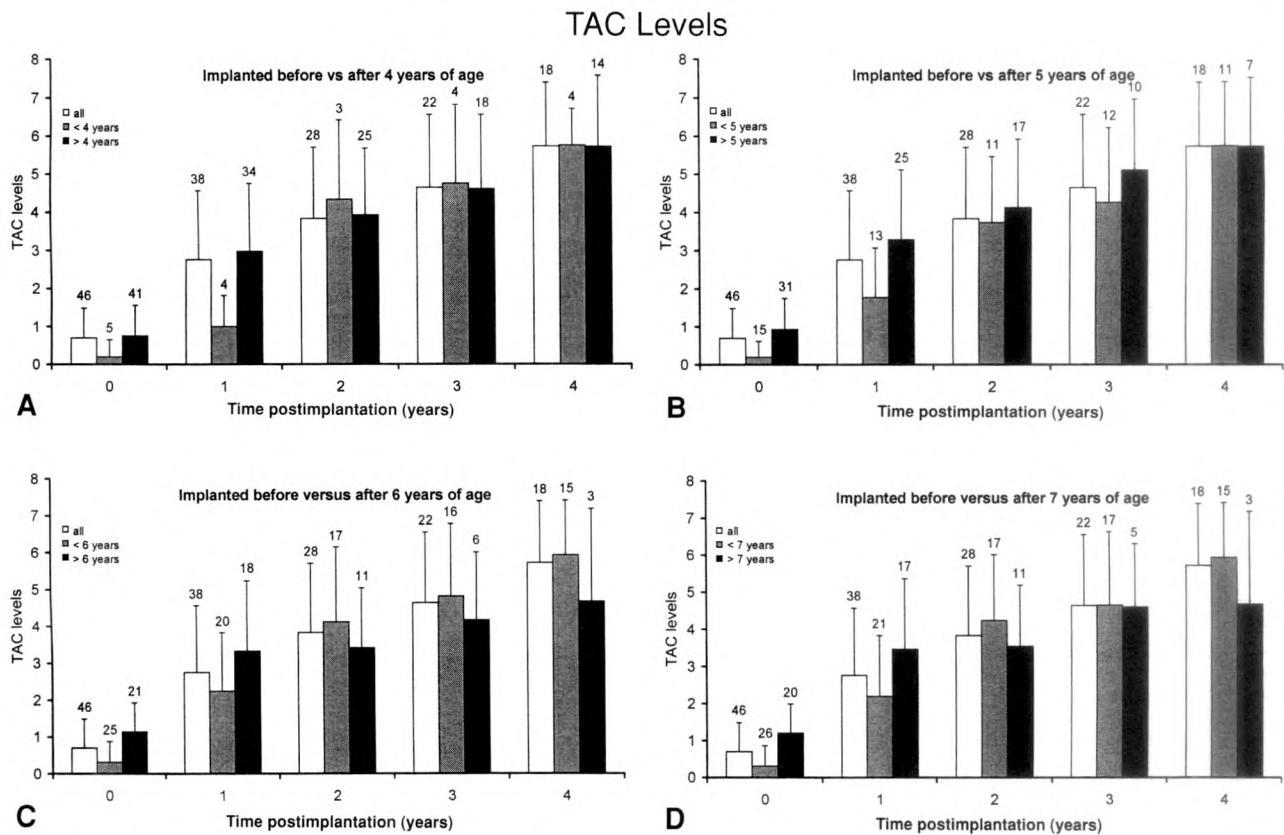


Fig 3. TAC (Test of Auditory Comprehension) test results. Data are presented in terms of average TAC level (0 to 8) achieved by subjects. Data format is same as in Fig 1.

same question in a slightly different way, asking whether there is a critical period during which the congenitally deaf child should be fitted with an implant to ensure a significant benefit from the cochlear implant device. Much of this discussion revolves, of course, around the issue of what the definition of "benefit" is. Some would regard an enhanced appreciation of environmental sounds as a benefit, whereas others would define benefit in terms of whether an individual can effectively improve oral communication with the cochlear implant device. Ultimately, one might ask whether the cochlear implant will allow open-set speech recognition.

In other studies, it has been shown that although children fitted with implants at younger ages do obtain better results in open-set tests than older-implanted children, at least some of these older children can have improved speech perception and therefore benefit from implantation. The question of an upper age limit for implantation in prelingually deaf subjects was explored in subjects from the age of 4 to 33 at the time of implantation.² In children given implants after the age of 12, there was some progress in the first year after implantation, but soon after, a plateau in performance was reached. Better scores were obtained in subjects given implants before the age of 8; children given implants between the ages of 8 and 11 showed intermediate scores. It has been suggested that children given implants at later ages need more time to achieve better results, ie, similar to those of children given implants at earlier ages, but our study does not confirm this,

at least for a 4-year postimplantation period. Indeed, in other data (not presented here, because the sample size is small), we found that on average, children fitted with implants after the age of 6 years demonstrated little improvement up to 6 years after implantation.

From this study, we conclude that on average, prelingually profoundly deaf children benefit the most from their implant if implantation is performed before the age of 6 years, as judged from their performance on a range of speech perception tests. In particular, they show steadily improving speech recognition in an open-set test, with no plateau reached more than 4 years after implantation. We realize, however, that although these results indicate a global tendency, it is still difficult to predict the results in a particular child. We see 6 years of age not as an absolute upper age limit for implantation in prelingually deaf children, but as a guideline to be considered with other factors in relation to candidacy, as well as a source of prognostic information for potential implant candidates and their parents.

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ASSESSING COCHLEAR IMPLANT BENEFIT IN VERY YOUNG CHILDREN

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Cochlear implants have become a widely accepted form of (re)habilitation for profoundly deaf children. Many centers around the world are placing implants in children at increasingly younger ages (ie, <2 years of age). Determining implant candidacy and implant benefit in young children, however, is a challenging task. Although identifying a sensorineural hearing loss in the severe-to-profound range can be achieved reliably in newborns, quantifying the amount of *functional* sensory aid benefit in this population is difficult to achieve. The purpose of this study was to examine the performance of 9 profoundly hearing-impaired infants on a procedure designed to assess functional auditory skills in young children, the Infant-Toddler: Meaningful Auditory Integration Scale (IT-MAIS).¹ Performance on this measure was assessed with hearing aids before implantation and again after 3 months of implant use.

METHODS

Nine prelingually deafened children, 18 to 23 months of age, who were fitted with implants during the clinical trial of the CLARION® Multi-Strategy™ Cochlear Implant participated in the study. All children demonstrated profound, bilateral, sensorineural hearing loss and negligible functional hearing aid benefit. Negligible functional hearing aid benefit was defined as no progress for at least 3 months on the IT-MAIS and a score no higher than 2 on questions 3, 5, and 6 of the IT-MAIS. Questions 3, 5, and

6 of the IT-MAIS assess the following auditory skills: 1) consistent and spontaneous response to name in quiet in everyday situations with auditory cues only (IT-MAIS question 3); 2) consistent and spontaneous alerting to environmental sounds in everyday situations (IT-MAIS question 5); and 3) consistent and spontaneous responses to new or unfamiliar sounds in everyday situations (IT-MAIS question 6).

The mean age at implantation was 20 months, and the mean age at onset of deafness was 2.2 months (range, 0 to 10 months). Seven children had congenital deafness, and 2 children presented with acquired deafness of unknown causes. The mean unaided pure tone average was 115 dB hearing level in the implant ear and 116 dB hearing level in the nonimplant ear. None of the children demonstrated a response to sound above 1,000 Hz in either ear. The mean length of hearing aid use at the time of implantation was 7.1 months (range, 4.1 to 13.5 months). Before implantation, the child's managing professional(s) was required to document a plateau in development. A plateau was defined as failure to pass basic auditory milestones after a minimum of 3 months of hearing aid use, coupled with enrollment in an intensive (re)habilitation program emphasizing development of auditory skills.

The IT-MAIS was used to assess functional auditory skills with hearing aids during the preoperative evaluation phase and with Clarion implants 3 months after im-

TABLE 1. NUMBER OF PATIENTS AND FREQUENCY OF DEMONSTRATION OF TARGET BEHAVIOR ON EACH PROBE OF IT-MAIS WITH HEARING AIDS

IT-MAIS Question	Probe	Score				
		Never ("0")	Rarely ("1")	Occasionally ("2")	Frequently ("3")	Always ("4")
1	Vocal behavior affected while wearing hearing aids?	7	0	2	0	0
2	Production of syllables and syllable-sequences recognized as speech?	8	1	0	0	0
3	Spontaneous alerting to name in quiet with auditory cues only?	9	0	0	0	0
4	Spontaneous alerting to name in noise with auditory cues only?	9	0	0	0	0
5	Spontaneous alerting to environmental sounds with auditory cues only?	9	0	0	0	0
6	Spontaneous alerting to sounds in new environments with auditory cues only?	9	0	0	0	0
7	Spontaneous recognition of sounds with auditory cues only?	9	0	0	0	0
8	Discriminates between two speakers' voices with auditory cues only?	9	0	0	0	0
9	Discriminates between speech and nonspeech stimuli with auditory cues only?	9	0	0	0	0
10	Responses to intonation (motherese) with auditory cues only?	9	0	0	0	0

Total number of patients is 9.
IT-MAIS — Infant-Toddler: Meaningful Auditory Integration Scale.

TABLE 2. NUMBER OF PATIENTS AND FREQUENCY OF DEMONSTRATION OF TARGET BEHAVIOR ON EACH PROBE OF IT-MAIS AFTER THREE MONTHS OF IMPLANT USE

IT-MAIS Question	Probe	Score				
		Never ("0")	Rarely ("1")	Occasionally ("2")	Frequently ("3")	Always ("4")
1	Vocal behavior affected?	0	0	1	7	1
2	Speech-like syllables?	0	3	6	0	0
3	Responds to name in quiet?	0	2	3	4	0
4	Responds to name in noise?	2	3	2	2	0
5	Alerts to environmental sounds?	0	1	7	1	0
6	Alerts to sounds in new environment?	0	2	6	1	0
7	Recognizes sounds?	0	4	4	1	0
8	Discriminates voices?	4	1	4	0	0
9	Discriminates speech vs nonspeech?	2	3	3	0	1
10	Responds to motherese?	2	3	3	1	0

Total number of patients is 9.

plantation. The IT-MAIS¹ is a criterion-referenced measure that employs a structured interview technique to obtain information from the parent(s) about the frequency with which the child demonstrates a set of 10 auditory or speech behaviors in everyday situations. The IT-MAIS is a modification of the Meaningful Auditory Integration Scale (MAIS),² a measure originally designed to assess the use of everyday listening skills in school-age children. Research has shown that the MAIS has high inter-rater reliability.² Additionally, performance on this measure is highly correlated ($p = .70$) with postoperative open-set word scores on the Phonetically Balanced-Kindergarten test in older children using multichannel implants.³ Items and criteria-response behaviors on the MAIS were modified to be more appropriate for infants and toddlers.

The IT-MAIS consists of 10 probes or questions (Table 1) that are used to query the parent about the frequency with which the child demonstrates target behaviors in everyday situations. On the basis of this information, the examiner assigns a rating consistent with the frequency of occurrence of each behavior using the following scoring system: 0 = never, 1 = rarely, 2 = occasionally, 3 = frequently, and 4 = always. Strict scoring criteria have been developed to ensure uniformity among examiners in scoring the parent's responses. Target behaviors are developmentally appropriate for infants and toddlers and include behaviors such as searching for the sound source, imitation of a sound, and responding to the cessation of sound. These behaviors precede the more overt auditory responses that older children demonstrate to sound.

RESULTS AND DISCUSSION

Preoperatively, with hearing aids, none of the children was assigned a score higher than 2 (ie, occasionally demonstrated the behavior) on any of the IT-MAIS probes. The majority of children were assigned a rating of 0 on the items (Table 1). The items on which the children were assigned a score above 0 (ie, 1 = rarely or 2 = occasionally) involved vocalization behaviors (probes 1 and 2). On the remaining 8 items, all children were assigned a rating of 0 (ie, never demonstrated the behavior), even after wearing hearing aids an average of 7 months. These results are not surprising, given the limited amount of residual hearing demonstrated by these children before im-

plantation. The data suggest that the youngest children being fitted with implants have the most profound losses, making candidacy decisions relatively more straightforward than in children who demonstrate some auditory capacity. A similar trend was reported by Waltzman and Cohen.⁴

After 3 months of implant use, a score of 1 or 2 (ie, occasionally or frequently demonstrating the behavior) was most often assigned on the items (Table 2). The data in Table 2 indicate that after 3 months of implant use, there was an increase in the percentage of patients who occasionally or frequently demonstrated the target behaviors for every probe. An examination of the data for individual patients revealed that every child showed an increase in the frequency of target behaviors on at least 7 of the 10 probes at the 3-month postoperative interval. Further improvement on all items is expected to emerge with more implant experience.

The results from the IT-MAIS suggest that measures of this nature yield valuable information for determining implant candidacy and implant benefit in infants and toddlers. Future research should include collection of longitudinal data in children with various degrees of hearing loss, and also normal-hearing infants. Because of the increasing number of very young children undergoing implantation, it is critical that a battery of objective and behavioral measures be identified to assess this population. The IT-MAIS should be viewed as a tool, as one of a battery of measures to adequately evaluate the whole child. Finally, these results should be viewed as preliminary and interpreted with caution because of the small sample size.

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PREOPERATIVE PREDICTORS OF POSTOPERATIVE IMPLANT PERFORMANCE IN CHILDREN

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INTRODUCTION

Although cochlear implants are widely accepted as a treatment option for profound deafness, children demonstrate a wide range of benefit from these devices. Research has shown that some children achieve a high level of speech recognition with a multichannel cochlear implant, whereas other children demonstrate more limited skills.¹⁻⁵ Identification of variables that contribute to postoperative performance differences is important to refining candidacy criteria and counseling parents about expected benefits. Previous studies have shown that the communication mode used by the child and the age at implantation make significant contributions to performance with an implant.^{1,4-8} These studies have shown that children who use oral communication achieve higher performance levels with their implants on speech perception tests than do children who use total communication (English-based sign system with auditory input).^{1,6-8} There also is growing evidence that children implanted at a younger age ultimately derive more benefit from their implants than do children implanted at an older age.^{4,5} The purpose of this report is to examine the preoperative variables that predicted postoperative speech perception skills in prelingually deafened children implanted with the CLARION® Multi-Strategy™ Cochlear Implant.

METHODS

Data were analyzed from 57 children who were implanted during the clinical trial of the Clarion device in the United States. The study group included all children with prelingual deafness for whom 12-month postoperative test results were available at the time of this report. The mean age at onset of deafness was 0.9 years, and the mean age at implantation was 5.4 years for the 57 children. The onset of deafness was prelingual in all children (ie, onset at <2 years of age). The mean preoperative pure tone average in the implanted ear was 110 dB HL. All children used the Continuous Interleaved Sampler strategy in their Clarion implants (1.2 device).

The Glendonald Auditory Screening Procedure (GASP)⁹ was chosen as the dependent variable because of the large range in performance on this measure after implantation. The GASP is an open-set word test with 12 words of different syllable number and/or stress pattern. The test was administered live-voice with auditory cues only.

In a preliminary analysis, the relationship between the following 12 independent variables and the 12-month GASP word score was examined: socioeconomic status, gender, communication mode (oral-cued speech or total communication), age at onset of deafness, age at which hearing aids were fitted, age at implantation, duration of deafness at time of implantation, preoperative unaided pure

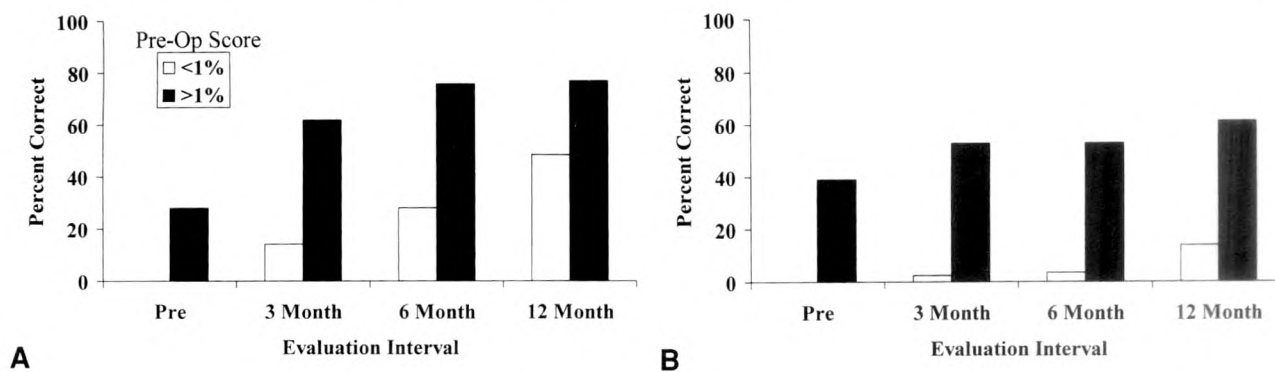
tone average in the implant and nonimplant ears, preoperative score in the implant and nonimplant ears on the Early Speech Perception Monosyllable Word Identification test,¹⁰ and preoperative GASP word score in the best-aided condition.

The results revealed that 2 preoperative variables were significantly related to 12-month performance on the GASP: 1) communication mode and 2) score on the GASP word test. Therefore, these 2 variables were selected for inclusion in a subsequent regression analysis. The results for children who used oral communication and cued speech were combined into 1 group (ie, oral), because previous analyses of preoperative and postoperative performance showed their performance to be similar. The communication mode was determined through parental inquiry and presumably reflected each child's style of communication in everyday situations. The ages at implantation were similar for children who used oral and total communication.

RESULTS

The results of the analysis revealed that communication mode ($\beta = -.427$, $p < .0001$) and preoperative performance on the GASP word test ($\beta = .467$, $p < .0001$) were significant independent predictors of the 12-month GASP score. Together, these 2 variables accounted for 43% of the variance in the 12-month performance on the GASP. To illustrate the effect of these findings on postoperative performance, we divided the children into 4 groups on the basis of communication mode and preoperative speech perception skills. Children who demonstrated a score of <1% on GASP word preoperatively were classified as having no open-set word recognition skills with hearing aids, whereas children who achieved a score of $\geq 1\%$ were classified as demonstrating at least some preoperative open-set word skills. The sample size for each group was as follows: 1) 15 children who used oral communication and demonstrated preoperative open-set skills; 2) 25 children who used oral communication and had no preoperative open-set skills; 3) 3 children who used total communication and demonstrated preoperative open-set skills; and 4) 14 children who used total communication and had no preoperative open-set skills.

The Figure, A, compares the children who used oral communication with and without preoperative open-set word recognition skills. After 12 months of implant use, the children who showed some open-set word recognition with hearing aids before implantation achieved a mean score of 77% (SD, 21%), compared with a mean score of 48% (SD, 34%) for the children with no preoperative open-set word skills. At the 12-month interval, the difference in performance between the 2 groups is smaller than



Mean preoperative and postoperative scores (percent) on GASP word test as function of preoperative speech perception score on GASP word test. A) For children who used oral communication ($n = 25$ GASP score $<1\%$; $n = 15$ GASP score $\geq 1\%$). B) For children who used total communication ($n = 14$ GASP score $<1\%$; $n = 3$ GASP score $\geq 1\%$).

at the earlier intervals, suggesting that the children with no open-set skills may be catching up to those children who received their implants at a time when they had better speech understanding abilities. The Figure, B, shows the data for children who used total communication. The differences between the 2 groups are even more pronounced than for the oral children (see Figure, A). The 12-month mean score of the children with open-set skills was 61% (SD, 53%), compared with a mean score of 14% (SD, 20%) for the children with no preoperative open-set word recognition. Unlike the children who used oral communication, however, the children using total communication without preoperative speech perception skills continue to demonstrate limited speech recognition skills after 12 months of implant use.

Comparing the 12-month data in the Figure, A,B, we see a much smaller difference between the oral children with preoperative speech perception skills (mean, 77%) and similar total communication children (mean, 61%) than between the oral children without preoperative speech understanding (mean, 48%) and similar total communication children (mean, 14%).

DISCUSSION

The results of this study are consistent with those of previous investigations showing that children who use oral communication achieve higher levels of performance on speech perception tests with their implants than do children who use total communication.^{1,6-8} The role of communication mode in determining implant outcome, however, needs to be interpreted with caution, given the many factors that affect selection of a communication mode and educational setting for children with profound hearing impairments. Selection of a communication mode and school setting is influenced by the educational options available to the parents and the characteristics of the child. In this study, only 3 children who used total communication preoperatively demonstrated open-set word skills (ie, score of $\geq 1\%$ on GASP). This finding suggests that few children with auditory potential before implantation use total communication. Moreover, the dichotomy between oral and total communication may become less clear over time as children who use total communication develop functional auditory-oral skills with their implants and become

more like oral communicators.

A new finding of this study is the contribution of preoperative speech perception abilities with hearing aids to postimplant performance. Although clinical intuition suggests that children with better preoperative speech perception abilities would continue to demonstrate higher levels of performance after implantation than children with more limited abilities, few, if any, studies have substantiated this notion with empirical evidence. This finding raises important questions regarding audiological candidacy criteria, including ear selection for implantation.

Unlike other studies, age at implantation was not found to be a significant predictor of postoperative implant performance. However, previous studies have reported that differences between children given implants at older and younger ages did not emerge until after at least 2 years of implant use. The children in this study had used their devices for only 12 months, so differences in implant benefit may emerge after the youngest children have had more implant experience.

Finally, the results of this study need to be interpreted with an understanding of the methodology employed to examine the variance among children in their postoperative performance with implants. This study was not designed to conduct a systematic comparison of children who use different modes of communication. Rather, data were analyzed from a large group of children who presented for implantation. Future studies are needed to identify other variables that contribute to implant success.

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COCHLEAR IMPLANTS IN INFANTS AND TODDLERS

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INTRODUCTION

Critical learning periods exist in early childhood that affect the ability of children to develop normal speech and language. Ruben¹ recently summarized the literature and found support for the hypothesis that a critical period for phonological development exists in the first 12 months of life. He suggests that phonology is the platform on which syntax and semantics are built, and if speech development is delayed by the sensory deprivation of deafness, then language will also be delayed. Not only does deafness limit or prohibit access to the phonetic code of spoken languages, it also diminishes the child's exposure to the rich and varied linguistic models that normally hearing children receive from listening to those around them talk. Because of the potentially deleterious impact of hearing loss on a child's speech and language development (among other areas), it seems logical that early diagnosis, treatment, and intervention would be critical for optimal outcomes. When hearing aids do not provide detection of conversational speech, it is not possible to develop the speech perception skills that typically assist

with speech and language development. In these cases, cochlear implants often have provided the auditory input that facilitates acquisition of speech and spoken language. Recent studies² (also Svirskey et al, this supplement, pp 128-130) have demonstrated that children with cochlear implants can develop language at normal rates, even though they are delayed at the onset. The current study was undertaken to determine whether children fitted with implants as infants or toddlers can develop speech and language at rates equal to or surpassing those of normally hearing peers and ultimately attain age-appropriate speech and language skills. Preliminary speech perception, speech production, and language data are here presented for 14 children who received cochlear implants between the ages of 9 and 25 months. The data are reviewed and surgical considerations are mentioned to highlight both the benefits and potential challenges of implantation in infants and toddlers.

MATERIALS AND METHODS

The subjects were 14 children ages 25 months or younger who received cochlear implants at the Carle Clinic As-

DEMOGRAPHIC INFORMATION ON 14 SUBJECTS

Subject	Cause of Deafness	Age at Implantation (mo)	Unaided PTA (dB)		Device*/Ear	Months of Follow-up
			Right	Left		
S1	CI	18	NR	NR	CI22/R	24
S2	CU	21	NR	NR	CI22/R	18
S3	CA	21	98	99	CI22/R	30
S4	CU	18	NR	NR	C 1.2/L	12
S5	M 4 mo	9	NR	NR	C S/R	6
S6	CU	12	114	115	C S/L	6
S7	CU	16	NR	NR	C S/L	6
S8	M 11 mo	20	NR	NR	CI22/R	12
S9	CU	24	NR	NR	C 1.2/L	12
S10	CU	24	122	118	CI24/R	6
S11	CA	24	106	106	C 1.2/R	24
S12	CA	25	105	110	CI24/L	12
S13	CU	25	112	116	C 1.2/R	24
S14	CU	24	NR	NR	CI22/R	36

PTA — pure tone average of 0.5, 1, 2, and 4 kHz, CI — congenital inherited, NR — no response, CU — congenital unknown, CA — congenital acquired, M — meningitis (age at onset in months).

*CI22 and CI24 are made by Cochlear Corporation; C S and C 1.2 are Clarion models made by Advanced Bionics Corporation.

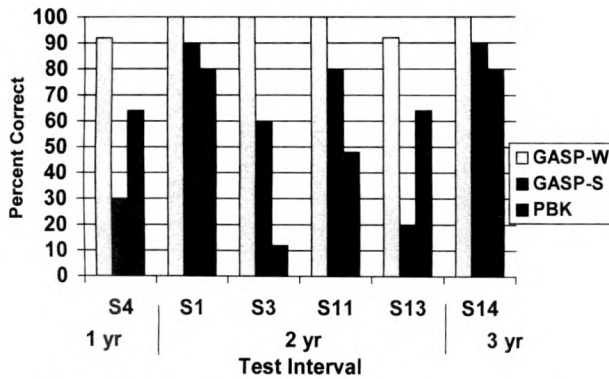


Fig 1. Speech perception scores for 6 subjects at 1-, 2-, and 3-year postoperative interval (most recent) on Glendonald Auditory Screening Procedure Word and Sentence tests (GASP-W, GASP-S), and Phonetically Balanced-Kindergarten (PBK) word list tests.

sociation and Carle Foundation Hospital. Five of the children were between 9 and 19 months of age (infants), and 9 were between 20 and 25 months (toddlers) at the time of surgery. Demographic data are summarized in the Table. For all children, the onset of deafness occurred when they were less than 1 year of age. Nine children used oral communication, and 5 used total communication. The cochleas were normal in all subjects, except for partial ossification in subject 8 and a mild deformity in subject 4. Generally, the poorer hearing ear was selected for implantation.

The surgical technique for the various devices (Cochlear Corporation CI22 and CI24M; Advanced Bionics 1.2 and S-Series) was essentially the same as that for older children, except for a few modifications. The incision was directed posterosuperior to the area that would become the mastoid tip (which is absent in young infants) to avoid injury to the facial nerve. The facial recess was normal in size, but because of the small mastoid opening in some of the infants, the approach was made from a more superior direction than usual, making the round window more difficult to visualize. Furthermore, because the skull is very

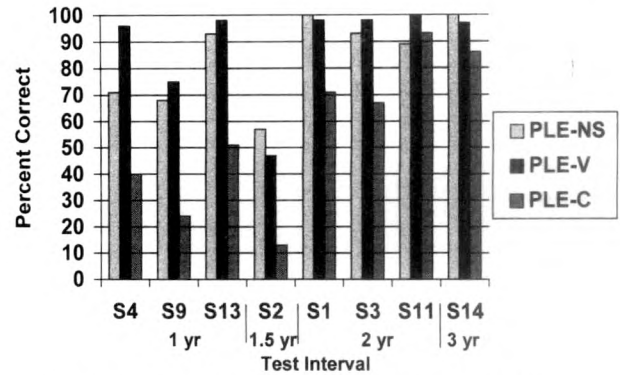


Fig 2. Speech production results for 8 subjects at 1-, 1.5-, 2-, and 3-year postoperative interval (most recent) on Phonetic Level Evaluation nonsegmental, vowel, and consonant (PLE-NS, PLE-V, PLE-C) tests.

thin and the internal receiver is relatively large, a bone island was created by drilling down to dura so the dura could be displaced by the receiver. Electrode impedance, electrical auditory brain stem response, and/or electrical compound action potential response were obtained through the implant during closure, not only to assess device functioning and/or neural integrity but also to assist with initial device programming.^{3,4}

Speech perception, speech production, and language skills were measured with tests most appropriate for age and ability. Speech perception measures included the Ling 6 Sounds Test,⁵ the Glendonald Auditory Screening Procedure (GASP-Word and Sentence),⁶ and the Phonetically Balanced-Kindergarten (PBK) word lists.⁷ Speech production was assessed with the Phonetic Level Evaluation (PLE).⁸ A modified scoring procedure was used for this test. The PLE was scored for nonsegmental speech features, for vowels in single and repeated syllables with the consonant sound "b" (eg, "ba" versus "bababa"), and for simple consonants, steps 1, 2, and 3 combined. Two points were given for consistent productions, 1 point was given for inconsistent productions, and no points were assigned

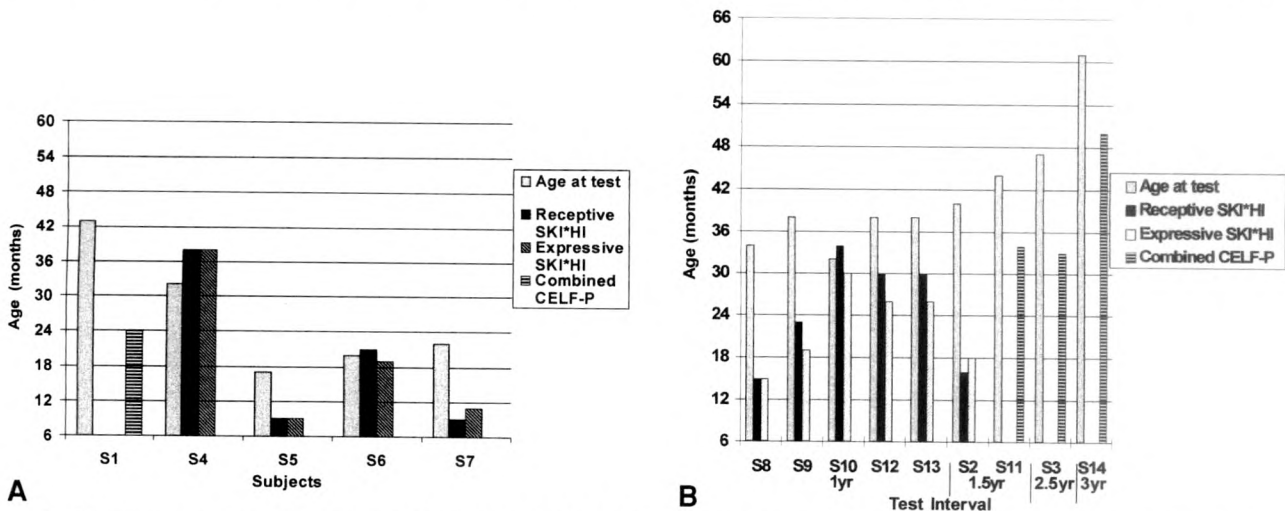


Fig 3. Language results. A) For 5 infants (age 9 to 19 months) at their most recent test intervals (age at test) on Skills for Hearing Impaired Children (SKI*HI) (subjects 4, 5, 6, 7) and Clinical Evaluation of Language Fundamentals-Preschool (CELF-P) (subject 1). B) For 9 toddlers (age 20 to 25 months) at their most recent test intervals on SKI*HI (subjects 2, 8, 9, 10, 12, 13) and CELF-P (subjects 3, 11, 14). Combined CELF-P — combined receptive and expressive scores.

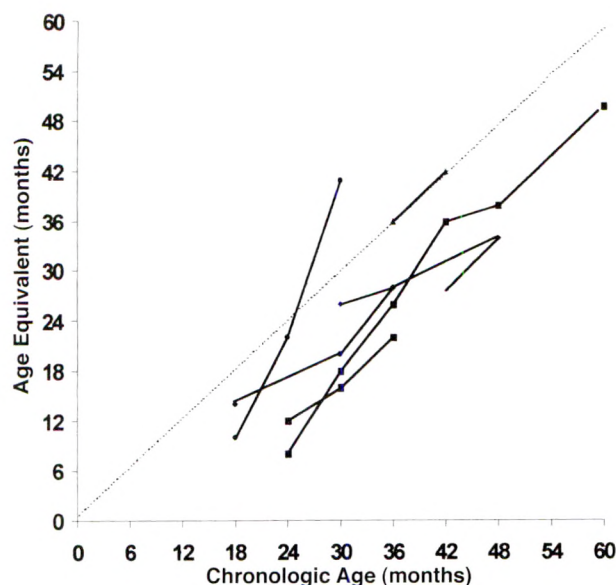


Fig 4. Sequential language results for 7 subjects who have been tested at more than 1 postoperative interval to show progress over time. Dotted diagonal line represents expected language progress by children with normal hearing.

if the child was unable to produce the target sound. For each section (nonsegmentals, vowels, and simple consonants, steps 1, 2, and 3 combined), percent accuracy was calculated by dividing the total number of points obtained by the total number of points possible. Language measures included the Skills for Hearing Impaired Children (SKI*HI)⁹ given by means of parent interview, and the Clinical Evaluation of Language Fundamentals–Preschool (CELF-P).¹⁰ The tests were administered in the child's main method of communication.

Before implantation, all subjects met the audiological criteria for cochlear implantation. Whereas 4 of the 14 subjects could detect low- and middle frequency Ling sounds, 10 subjects detected only /a/ or could not detect any sounds when aided. Thirteen of the 14 subjects could not provide an imitative response for the PLE assessment. Subject 4 had a nonsegmental score of 36% and vowel and simple consonant scores of 7% and 3%, respectively. At the pre-implant interval, subjects 10 and 12 had age-appropriate language skills using total communication when assessed with the SKI*HI. The remaining subjects, regardless of communication method, had delays of at least 6 months and as great as 19 months.

RESULTS

All subjects had full insertions of their cochlear implant devices and were discharged on the day of surgery. There were 2 surgical complications: a temporary facial paralysis and a device migration resulting from an infection in the early postoperative period. Neither event was believed to be related to the subject's age at implantation. All 14 subjects were fitted with the external equipment approximately 4 weeks after surgery. At the most recent test interval, sound field audiograms demonstrated detection thresholds for narrowband noise at 25 to 35 dB hearing level for 0.25 to 4 kHz, and all subjects could detect

the 6 Ling sounds. Figure 1 summarizes the results for the GASP word, GASP sentence, and PBK tests for the subjects with at least 1 year of implant use. Six subjects (S4, S1, S3, S11, S13, and S14) at 1 year after implantation had GASP word scores of 90% or greater, and 5 of 6 subjects had PBK scores of 48% or greater. Four subjects (S2, S8, S9, and S12) were not able to provide a response to an open-set speech perception stimulus. Figure 2 shows speech production results for the PLE test for the 8 of the 14 subjects with at least 1 year of implant use. Seven of the 8 subjects had nonsegmental and vowel scores greater than 50%, and 6 of the 8 had vowel scores greater than 90%. Subjects 8 and 12 had 1 year of implant use, but were unable to provide the imitative response necessary for assessment. Subjects with 2 or more years of implant use demonstrated scores of 65% or higher for consonants on the PLE.

Figure 3 illustrates the language data for children given either the SKI*HI or the CELF-P measures. It can be observed from Fig 3A that 3 of the 5 subjects fitted with implants at 9 to 19 months (infants) had language levels at or above their chronological age. In Fig 3B, 8 of the 9 subjects fitted with implants at 20 to 25 months (toddlers) had delays in language that ranged between 8 and 20 months for either receptive or expressive language. Figure 4 shows the language progress over time for 7 children who had SKI*HI or CELF-P tests at 2 or more intervals. The data indicate that the children are making language progress at rates comparable to those of their hearing peers.

DISCUSSION

From a surgical standpoint, the current generation of cochlear implants can be inserted relatively safely and successfully in infants and toddlers, with only minor modifications of standard pediatric implant techniques. The subject given an implant at 16 months had a head circumference of 40.5 cm, equivalent to the head size of an average 4-month-old girl. The 9-month-old subject had a head circumference of 44 cm (equivalent to the 25th percentile for a 9-month-old boy and the 50th percentile for a 6-month-old boy). The results suggest that head size and mastoid development are of greater surgical concern than chronological age. Therefore, if CT scanning indicates sufficient mastoid development, successful implantation might be possible for children younger than 6 months.

The concept of critical periods in early childhood in which certain neurologic processes develop has become an increasingly important consideration for early implantation. With steadily improving technology, clinicians' ability to identify and treat hearing loss has given children with hearing impairment increased chances of successful auditory input, resulting in the possible development of oral communication at earlier ages. Recent data presented by C. Yashinoga-Itano (unpublished observations) suggest that identification of hearing loss and intervention at 6 months of age or less results in higher language levels than would be attained by children beginning services after 6 months of age. The data from the present study suggest that early implantation (before age 2) gives children with

profound hearing loss sufficient auditory input to assist in development of improved speech and language skills, and that implantation before 18 months of age may further expedite this process. In 1997, Miyamoto et al² reported that deaf children with implants made approximately 12 months' expressive language progress per year, whereas those without implants made 5 months' gain during the same period. The results of the present study also suggest that some children progress at a normal language acquisition rate after implantation. If this is so, cochlear implantation at a younger age would conceivably result in fewer delays, because the language gap is narrower at the onset of treatment. Experience with the children in this study demonstrates that children can successfully receive a cochlear implant as early as 9 months of age and that although surgical modifications may be necessary, implants can be applied successfully in the younger pediatric population.

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SPEECH PERCEPTION BY CHILDREN WITH THE CLARION (CIS) OR NUCLEUS 22 (SPEAK) COCHLEAR IMPLANT OR HEARING AIDS

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INTRODUCTION

Recently we examined the speech perception abilities of children with profound prelingual hearing loss acquired before the age of 3 who used either multichannel cochlear implants (CIs) or hearing aids (HAs).^{1,2} Speech perception scores for children who used CIs were compared to predicted scores from children who used HAs. The predictions for HA users were obtained by performing linear regression analyses of speech perception scores as a function of age. In the first study,¹ we examined both closed- and open-set speech perception in children who use the Nucleus 22 cochlear implant. Few of those children used the spectral peak (SPEAK)³ processing strategy, and many of them changed devices over time. Nevertheless, by approximately 3 to 5 years of implant use, the average speech perception scores of the children using CIs surpassed those predicted for the children using HAs who had pure tone average (PTA) hearing (at 500, 1,000, and 2,000 Hz) of 90 to 100 dB hearing level (HL).

In the second study,² we examined the speech perception of all of the children in the United States with profound prelingual hearing loss who received Clarion implants before the age of 12 and participated in the clinical trials for US Food and Drug Administration approval. All of the children had used the Continuous Interleaved Sampler (CIS) processing strategy⁴ since implantation. In that study, we examined open-set word and phoneme recognition on the Phonetically Balanced—Kindergarten (PBK) test.⁵ The average scores for the CI users reached the av-

erage levels predicted for the HA users with PTAs between 90 and 100 dB HL by approximately 12 to 18 months of implant use.

In the present study, we examined the speech perception abilities of children with profound prelingual hearing losses who had received an implant before the age of 6 and had used a single, state-of-the-art speech processing strategy (SPEAK or CIS) since implantation. The average performance over time by these 2 groups of CI users was then compared with the average predicted performance for HA users. In addition, we compared the speech perception scores of the 2 groups of CI users. The comparisons were made only between children using the same form of communication, either oral communication (OC) or total communication (TC; the simultaneous use of signed and spoken English).

METHODS

Participants. The HA group consisted of 26 children with prelingual profound hearing losses with PTAs between 90 and 100 dB HL (HA90-100) in their better ear. Sixteen used OC, and 10 used TC. The mean age at onset of deafness and age at the time the hearing aids were fitted did not differ as a function of communication mode. The children were between 2 and 15 years of age at the time of testing.

All CI children had prelingual profound hearing losses and had received a CI before the age of 6. Forty children had received the Nucleus 22 implant and had used the

AGES AT ONSET OF PROFOUND HEARING LOSS AND AT INITIAL FITTING WITH DEVICE, AND PTA, FOR EACH EXPERIMENTAL GROUP

Group	Age at Onset (y)		Age at Fitting (y)		PTA in Better Ear (dB HL)	
	OC	TC	OC	TC	OC	TC
Nucleus implant	0.3 ± 0.6 (0.0-2.1)	0.1 ± 0.4 (0.0-1.5)	3.2 ± 1.1 (1.5-5.3)	3.3 ± 1.0 (1.8-5.3)	110 ± 1.0 (100-120)	110 ± 1.0 (100-120)
Clarion implant	0.3 ± 0.6 (0.0-2.5)	0.2 ± 0.5 (0.0-2.5)	3.2 ± 1.1 (1.6-5.8)	3.3 ± 1.2 (1.5-5.9)	110 ± 1.0 (100-120)	110 ± 1.0 (100-120)
HA ₉₀₋₁₀₀	0.1 ± 0.3 (0.0-1.0)	0.5 ± 0.8 (0.0-2.5)	1.9 ± 1.1 (0.2-5.0)	1.4 ± 0.9 (0.3-3.0)	110 ± 1.0 (100-120)	110 ± 1.0 (100-120)

Data are mean ± SD, with range in parentheses.
PTA — pure tone average, HL — hearing level, OC — oral communication, TC — total communication, HA₉₀₋₁₀₀ — hearing aid group with PTAs of 90 to 100 dB HL.

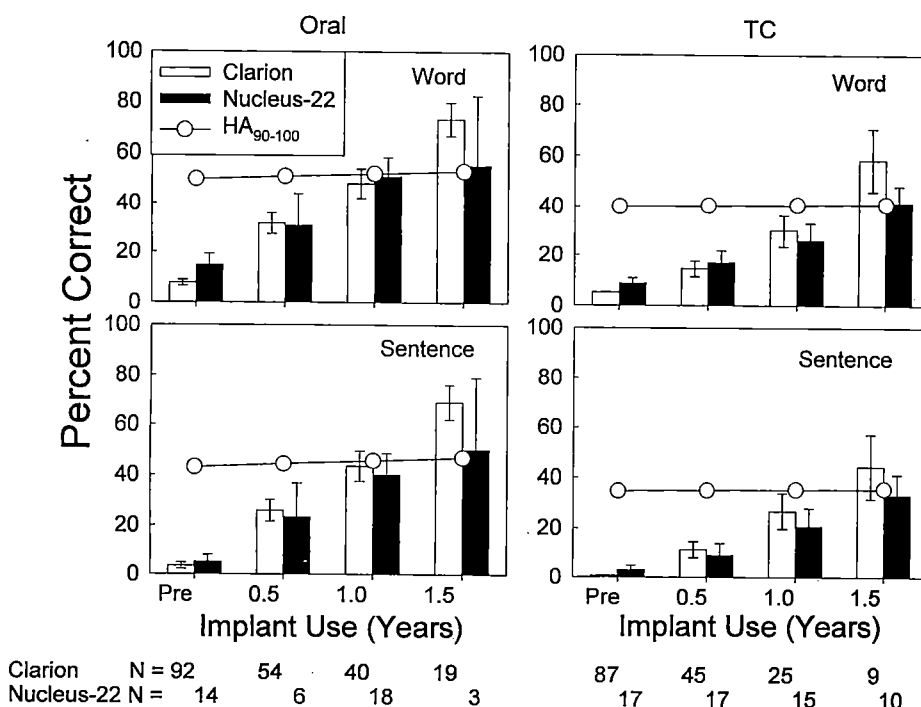
SPEAK strategy since implantation. Twenty of these children used OC, and 20 used TC. Of the 179 children who received the Clarion implant and used the CIS strategy, 92 used OC and 87 used TC. The average age at onset of deafness, the average age at implantation, and the average PTA in the better ear were virtually identical for the 2 groups of CI users (see Table).

Speech Materials. The children were given a variety of speech perception tests. For the present analysis, one measure (Mr Potato Head test⁶) was selected, as this was given to virtually every CI user. The Mr Potato Head test is a 10-item modified open-set test of speech perception appropriate for young children. The children respond to the sentences by placing items on a toy called Mr Potato Head or by making Mr Potato Head perform specific tasks. The test is scored for total sentences and number of key words correct. The test is administered in an auditory-only mode via live voice at approximately 70 dB sound pressure level by an experienced audiologist or speech pathologist.

Testing Intervals. The children who used the Nucleus implant were tested preoperatively and at 6-month or yearly intervals by 1 of 7 speech-language pathologists or au-

diologists. The children who used the Clarion implant were tested before and 3, 6, 12, and 18 months after implantation at 1 of approximately 20 sites. The average ages at onset of deafness, age at implantation, and average PTA in the better ear were virtually the same for the 2 groups of CI users (see Table).

Statistical Analysis. A linear regression analysis of speech perception scores as a function of age at testing was carried out for the children who used HAs to assess the effects of maturation on speech perception scores in the absence of implantation. Some of the children who used HAs were young enough to be given the Mr Potato Head test, and the rest were given the PBK test. If the child was given the Mr Potato Head test, that score was used. If the child was given the PBK test instead, performance on the Mr Potato Head test was estimated from performance on the PBK test. Previous data collected in our laboratory demonstrated a strong positive linear correlation (r of approximately +.90) between performance on the PBK and Mr Potato Head tests for children with profound prelingual hearing losses who used either CIs or HAs (unpublished observations). Regressions were carried out separately for OC and TC.



Percent correct on Mr Potato Head test versus duration of cochlear implant (CI) use. Word scores are shown in top panels, and sentence scores are shown in bottom panels. (Chance performance is 0% correct.) Data from children in oral communication programs are shown in left 2 panels, while data from children in total communication (TC) programs are in right 2 panels. Error bars are standard error of mean. Number of CI users tested is listed below each testing interval. Data from hearing aid users are predictions from linear regressions based on average age of children using CIs at each testing interval.

RESULTS

As illustrated in the Figure, the average scores for the CI users were very low before implantation, regardless of communication mode or device. Within each mode of communication, the average performance of the children who used implants improved at a faster rate than the predicted performance of the children who used HAs. For the children who used OC, the average performance of CI users approached the average predicted performance of the children in the HA90-100 group after 12 to 18 months of implant use. For the children who used TC, the average performance of the children who used implants approached the average predicted performance of the children in the HA90-100 group after 18 months of implant use.

No significant differences were found at any test interval between the 2 groups of children who used implants (Clarion and Nucleus users). The average performance levels were very similar for these 2 groups of children up to 12 months after implantation. At the 18-month testing interval, the average performance of the children who used the Clarion implant was approximately 15% higher than the average performance for the children with the Nucleus implant. However, because of the small sample size and the large amount of intersubject variability, this difference was not statistically significant for either mode of communication (ie, for the children who used TC, $t = 1.24$, $p = .233$). Further longitudinal studies with larger numbers of children may yet reveal differences in performance with the 2 devices.

DISCUSSION

We compared the performance of children who had used the latest speech processing strategies continuously since implantation for the 2 implants currently approved for use in children in the United States: the Clarion device and the Nucleus device. In the present study, after 12 to 18

months of implant use, the average speech perception scores for children with implants matched the scores predicted for HA users with PTAs between 90 and 100 dB HL. It is encouraging that this level of speech perception was achieved much faster than was found in studies examining children given implants at later ages and using prior generations of stimulation strategies.¹ However, in this study, some of the scores from HA users were predicted on the basis of their PBK scores. To remove this layer of unnecessary complexity, future studies should administer the Mr Potato Head test to larger groups of HA users. In addition, as CI technology improves, it may become important to compare the speech perception of pediatric CI users with that of children with hearing losses in the severe range (70 to 90 dB HL), some of whom may become candidates for cochlear implantation in the future. Audiological criteria for implantation clearly warrant further examination, and the criteria will certainly change as the scientific knowledge in this area increases.

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RELATIVE IMPORTANCE OF RATE AND PLACE: EXPERIMENTS USING PITCH SCALING TECHNIQUES WITH COCHLEAR IMPLANT RECIPIENTS

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Pitch scaling was used to determine the dependence of perceived pitch on rate and place of stimulation in postlingually deafened adult subjects using cochlear implants. For stimulation rates below about 500 pulses per second (pps), perceived pitch is a strong function of both rate and place. In this range, perceived pitch increases logarithmically with stimulation rate, but decreases with distance from the round window. A 2-mm displacement into the cochlea has an effect similar to that of halving the stimulation rate. Place resolution in this context is comparable with the interelectrode spacing (0.75 mm). At rates approaching 1,000 pps, rate has little effect on perceived pitch. An average of bipolar quality judgments showed that periodic pulsatile stimulation is least pleasant when low frequencies are applied to the region closest to the window.

INTRODUCTION

Cochlear implants (CIs) work well for speech comprehension, but poorly for music perception and recognition.^{1,2} A project to improve music perception by CI users inspired this study of the way in which musical pitch depends on rate and place of stimulation. However, this question has broader scientific implications, because of the long-standing debate over the way in which pitch is coded in the normal ear. This debate continues because rate and

place of stimulation are strongly correlated in the normal ear. With a CI, however, rate and place of stimulation can be controlled almost independently.

Most speech processing strategies perform poorly with music, because they extract formants and other low-resolution features of the spectrum or spectral envelope. These strategies include multipeak and continuous interleaved stimulation and are described elsewhere.³ Most of these strategies map different, relatively broad ranges of fre-

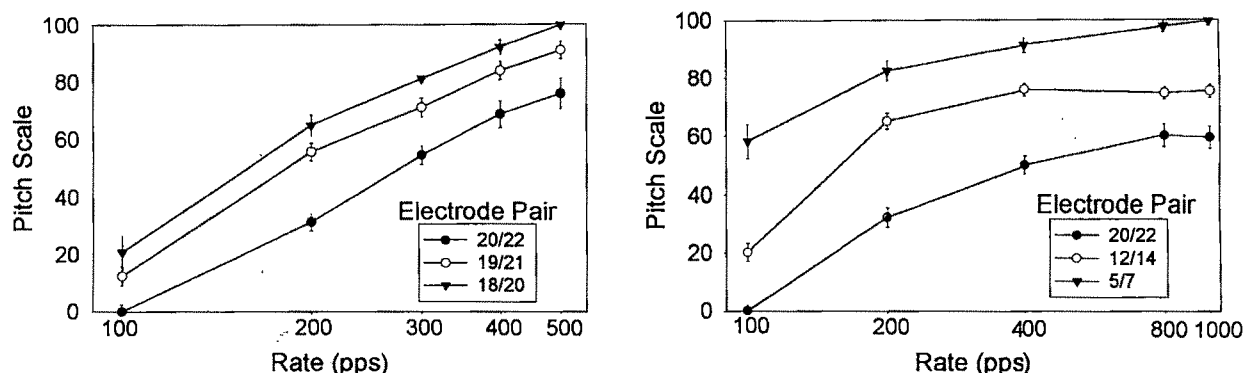


Fig 1. Average of pitch scaled values for all subjects ($\pm$ SEM). Higher-number electrodes are those inserted further (more apical), while lower-number electrodes are those closer to window end of cochlea (more basal). A) For each of 3 pairs of electrodes used, spacing between active electrodes was 0.75 mm. B) Larger range of rate and place.

quency to different electrodes and thus stimulate different regions of the cochlea. Several recent strategies stimulate at an arbitrary rate. This low resolution in the frequency domain and low information content in the time domain result in poor pitch perception and thus in poor perception of melody and harmony in music.

Studies using CIs to elicit pitch have concentrated on the rate⁴ and place⁵ of stimulation. Other techniques that affect pitch are the modulation of 2 rates,⁶ the nonsimultaneous aggregation of 2 rates,⁷ varying the pulse width,⁸ and varying the amplitude of stimulation.^{9,10} In the rare case in which a subject has both an implant and some residual acoustic hearing in the unimplanted ear, it is possible to do pitch matching experiments. Dorman et al¹¹ found that both the electrode number and the electrode stimulation frequency correlated strongly with the frequency of a matched acoustic stimulus.

This study uses the technique of pitch scaling^{12,13} (described below), which has the advantages that it does not require musical training and that subjects are not asked to adjust stimuli to "match" percepts that may differ in more than 1 perceptual dimension.⁴

METHODS

Six postlingually deafened adults volunteered for this study, which comprised 3 test sessions lasting 1 to 2 hours. Their ages ranged from 35 to 72 years, and all had been implanted with a Nucleus CI22 multichannel device for between 2 and 11 years. All used the "bipolar + 1" mode, in which the stimulated electrode pair are separated by 1 temporarily inactive electrode. This mode was used in these experiments.

The stimuli were 1,000-ms pulse trains of biphasic rectangular pulses. The pulse durations were 100 μ s with a 25- μ s interphase gap. The stimuli were presented by way of purpose-written testing software on a computer and a SPrint processor. The subjects adjusted all stimuli to equal loudness before testing began.

A pitch scaling technique^{12,13} was followed. Subjects assigned a value on an arbitrary scale from 0 (very low pitch) to 100 (very high pitch). The presentation order was randomized, and all stimuli were presented twice in a training block before data collection. Then, all stimuli

were presented 7 times in each data gathering block. The first pitch scale value for each stimulus was discarded to allow for an initial adjustment period.¹² Each subject's values were then converted to a percentage of the total scale range that he or she used during that series of experiments to allow comparison among subjects. The same protocol was used in 2 separate experiments conducted over different ranges of rate and electrode position.

After each of the pitch scaling tests, each stimulus was presented twice and the subject was asked to assess the quality or timbre of the sound by indicating a position on a line between pairs of bipolar quality words: like-dislike, mechanical-natural, pleasant-unpleasant, clear-fuzzy, musical-not musical, natural-unnatural, colorful-colorless, and brilliant-dull. A mean of these positions was taken to give a quality rating of the sound for that subject.

RESULTS AND DISCUSSION

One series of measurements used rates of 100 to 500 pulses per second (pps) delivered to the 3 closely spaced electrode pairs furthest from the window (most apical). Over this range, perceived pitch varies logarithmically with stimulation rate (Fig 1A). This invites a comparison with normal hearing, in which, for pure tones, pitch varies logarithmically with acoustic frequency. Perceived pitch depends on place in the expected sense, decreasing with increasing distance from the window end. (This result is in qualitative agreement with the pitch matching experiments of Dorman et al.¹¹) In Fig 1A, the 3 electrode pairs are at separations of 1 electrode spacing or 0.75 mm. Therefore, a displacement of 2 electrode spacings has an effect slightly less than that of doubling the stimulation rate. The differences between electrode pairs 18-20 and 19-21 is significant at .05; this finding suggests that place resolution of 1 electrode spacing is possible in this context.

Figure 1B shows the results for a larger range of rate and place. Again, pitch decreases with increased distance of the electrode from the window. Pitch increases with stimulation rate over the range 100 to 500 pps, but above this rate, there is little further increase in pitch with rate, especially for the electrodes closest to the windows. This apparent saturation with stimulation rate may be related to the maximum firing rate of nerve fibers.

Together, these results suggest that for cochlear implant

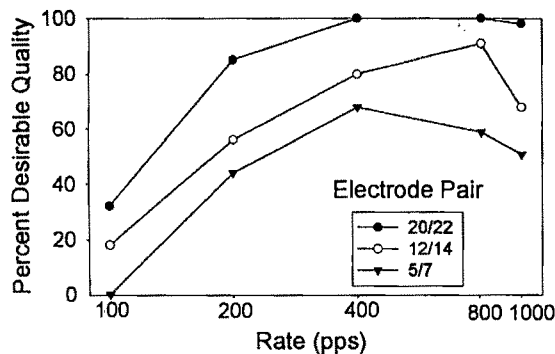


Fig 2. Subject quality ratings.

subjects using pulsatile stimulation, both rate and place contribute to pitch for low stimulation rates, but place dominates at higher rates. The subjects in this study do not, of course, have normal hearing, so the implications of these results for the rate-place debate in general are limited, but they are nonetheless suggestive.

The subjects' sound quality reports (Fig 2) suggest that periodic pulsatile stimulation is least pleasant when low rates are applied to the region closest to the windows, ie, that region normally associated with high pitch. This is unsurprising: these postlingually deafened subjects may have been comparing the implant stimulation with a remembered, or perhaps innate, rate-place correlation.

These results suggest that combinations of rate and place, especially at low frequencies, may be best suited to conveying pitch in processing strategies designed for music. The results also put a lower bound (approximately 0.8 mm) on the capacity of the ear to resolve electrode position in the context of musical pitch, which suggests that a large number of closely spaced electrodes have considerable advantages for pitch perception in the region above several hundred pulses per second.

CONCLUSIONS

Perceived pitch is a strong function of both rate and place for stimulation rates below about 500 pps. In this region, perceived pitch increases logarithmically with stimulation rate. Perceived pitch also decreases with distance from the window, with a 2-mm displacement having an effect similar to that of halving of stimulation rate.

At frequencies approaching 1,000 pps, rate has little effect on pitch. An upper bound to the resolution of electrode position in the context of pitch judgment is comparable with interelectrode spacing (0.75 mm) in the array used here.

ACKNOWLEDGMENTS — Thanks to our tireless volunteers for their time and patience, to Stephanie Shaw and Paul Carter of Cochlear Ltd, and to Kate Gfeller for the bipolar quality words.

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CHANGES IN STIMULATION LEVELS OVER TIME IN NUCLEUS 22 COCHLEAR IMPLANT USERS

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The purpose of this study was to evaluate changes that occur over time in the electrical stimulation levels of cochlear implant users. A retrospective review of program summaries for 26 postlingually deafened adult Nucleus cochlear implant users was completed. Program summaries were used to assess changes in electrical stimulation at threshold (T) and maximum comfort (C) levels. Comparisons were made at intervals including the subject's initial stimulation and 2-week, 3-month, 6-month, 1-year, and most recent programming sessions. Five patients had 5 years or more of implant use; 8 patients had 3 to 5 years or more of implant use; and the remainder had been using their implant for 2 to 3 years. No patient with less than 2 years of implant use was included. Results indicated that changes in stimulation levels occur gradually over time. Although the changes in stimulation levels from one programming session to the next were not significant, the changes in current requirements for both T and C levels were found to be significant when we compared the 6-month and most recent programming intervals.

INTRODUCTION

Accurate setting of threshold (T) and maximum comfort (C) levels is necessary for maximizing the benefit derived from a multichannel cochlear implant. Opinions differ as to how often implant users need to have their programming reevaluated in order to maintain accurate settings. It is well accepted that in the early weeks of implant use, significant changes in current levels may occur but that after a period of adjustment, T and C levels stabilize. The general consensus in the implant community seems to be that current levels stabilize between 3 and 6 months for most adult cochlear implant recipients. Minor adjustments may be made over time, but the general trend is for stimulation requirements to remain relatively fixed over time. When changes do occur, there is often speculation about a shift in electrode position, a device malfunction, or development of ossification in the cochlea.

Early research¹ reported that thresholds of electrical stimulation tended to increase in macaque monkeys implanted with various types of intracochlear multichannel or single-electrode arrays and followed for periods of up to 8 years. Eddington et al² reported on the threshold to electrical stimulation in 2 patients implanted with multichannel electrode arrays over a period of approximately 2 years. In that report, the researchers concluded that there was no change in electrical stimulation levels over the

study period. Research is not yet available that assesses changes in electrical stimulation levels after long-term use of intracochlear electrode arrays in human subjects. Such information would prove helpful in determining the frequency of programming necessary to maintain optimal stimulation levels. It is also important to track changes over time as durations of implant use increase, because it is unknown how electrical stimulation requirements may change over the course of the lifetime of an implant recipient.

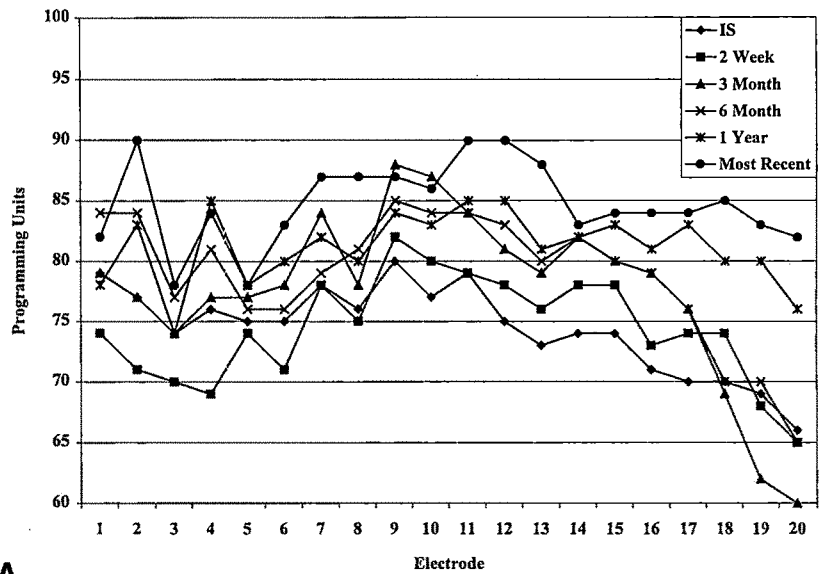
METHODS

Twenty-six postlingually deafened adult patients implanted with the Nucleus 22 cochlear implant at the University of Miami Ear Institute between 1990 and 1995 were included in this study. The subjects ranged in age from 34 to 81 years, with a mean age of 61.7 years, at the time of implantation. All subjects had at least 2 years of implant usage. The mean length of implant use was 3.32 years, with a range of 2 years to 7.5 years. The origins of hearing loss included genetic causes (6), otosclerosis (3), illness (3), Meniere's disease (2), ototoxic medication (2), trauma (1), and unknown causes (9). The demographic information for each subject is summarized in Table 1.

All subjects had full insertions of the internal electrode array, with an average insertion of 6 of 10 stiffening rings. All subjects used the MSP or SPECTRA speech proces-

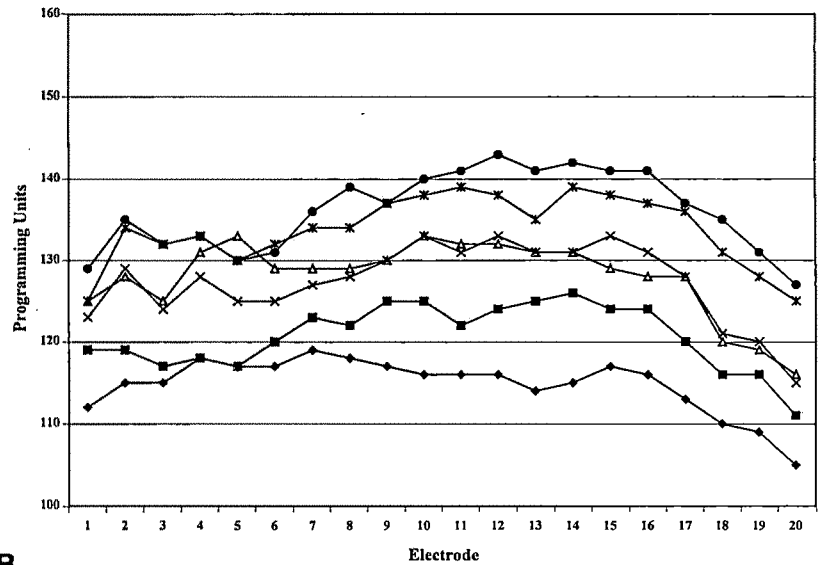
TABLE 1. SUBJECT DEMOGRAPHIC DATA

Subject	Age at Implantation (y)	Cause of Deafness	Length of Implant Use (y)	Electrode Insertion	Active Electrodes		Initial to Recent Map (mo)	Change From 6 mo to Most Recent	
					Initial Stimulation	Most Recent		T Level	C Level
S1	36	Meniere's	7.5	22+10	18	19	41	2.4	-1.37
S2	72	Familial	4	22+10	20	20	38	18.8	5
S3	72	Familial	2	22+7	17	17	7	-12	-17
S4	71	Genetic	2.1	22+1	20	15	19	0.97	14.54
S5	67	Unknown	2.5	22+6	16	15	27	24.1	9.66
S6	64	Ototoxic medication	3	22+1	18	17	28	-17.7	-1.37
S7	29	Illness	3	22+6	15	14	33		
S8	80	Unknown	2	22+6	20	14	13	-11.6	-37
S9	70	Unknown	2.2	22+4	20	20	17	6.3	-4.05
S10	76	R auditory nerve	5	22+8	19	19	27	0.54	-10.48
S11	65	Illness	3.3	22+6	20	17	37	5.6	12.6
S12	52	Trauma	2.5	22+10	19	18	29	11.4	42
S13	68	Otosclerosis	2.8	22+7	14	17	28		
S14	46	Unknown	2.7	22+5	18	18	24	13.78	14.05
S15	56	Meniere's	2.7	22+5	20	20	31	14.5	16.2
S16	57	Unknown	3.3	22+5	19	17	44	2.6	3.1
S17	59	Unknown	2.4	22+5	17	17	30	25.7	35.8
S18	43	Illness	2.2	22+5	20	20	3		
S19	81	Otosclerosis	2.1	22+10	18	16	9	1.5	6.93
S20	76	Unknown	2	22+7	18	19	14	-0.03	12.97
S21	57	Otosclerosis	2	22+8	18	19	19	11.47	8.58
S22	61	Familial	6.6	22+3	20	20	41	14	36.4
S23	72	Ototoxic medication	7.4	22+10	20	18	48	28.6	42.67
S24	60	Unknown	5.1	22+5	18	17	52	24.92	38.94
S25	34	Unknown	3.2	22+4	20	14	32	0.42	7.06
S26	80	Genetic	3	22+4	18	16	24	9.3	-2.49
Average	61.69		3.33	22+6	18.46	17.42	27.5	7.63	10.12



Mean stimulation levels at A) threshold level and B) maximum comfort level. IS — initial stimulation.

A



B

sors and had remained in the same programming mode for all visits. Twenty-four subjects used a bipolar + 1 programming mode, 1 used a common ground mode, and 1 was programmed in a bipolar + 3 mode. Subjects were excluded if the programming mode changed. One patient, excluded on the basis of a frequently repeated unexplainable fluctuation in both T and C levels, was ultimately determined to have a failed internal device. The average number of active electrodes was 18 at the time of initial stimulation and 17 electrodes for the most recent program.

A retrospective record review was utilized to gather the data for this study. Program summaries for subjects' initial stimulation and 2-week, 3-month, 6-month, 1-year, and most recent programming visits were reviewed. Although all subjects had at least 2 years of implant use, summaries for each of the visits could not be obtained for every subject. The T and C levels at the time of each visit were recorded into a statistical analysis program. Changes in electrical stimulation levels between each programming

session were analyzed. The changes were evaluated both within subjects and as group averages. In addition, the electrode array was separated into basal, medial, and apical sections. The basal portion of the electrode array included electrodes 1 through 6, the medial section utilized electrodes 7 through 14, and electrodes 15 through 20 were considered the apical portion of the array. The T and C levels were averaged for each section and compared between the 6-month session and the most recent programming session to ascertain whether basal, medial, or apical locations were more susceptible to change. We used *t*-tests to assess the statistical significance of changes. Regression analyses were used to determine whether a relationship existed between the length of device use and the degree of stimulation changes. Although the numbers were small, the relationship between cause of deafness and degree of change was evaluated.

Measurements of threshold levels for the subjects in this study were obtained by means of a bracketed tech-

TABLE 2. MEAN STIMULATION AND SIGNIFICANCE LEVELS FOR AVERAGED BASAL, MEDIAL, AND APICAL ELECTRODES

APICAL ELECTRODES			
	<i>Mean Stimulation Levels</i>		
	<i>6 Months</i>	<i>Most Recent</i>	<i>p</i>
T levels			
Apical (1-6)	79.6667	82.5	.0119
Medial (7-14)	82.25	87.25	.027
Basal (15-20)	71	83.667	.0235
C levels			
Apical (1-6)	128.5	135.3	.094
Medial (7-14)	130.5	139.9	.0006
Basal (15-20)	124.67	131.7	.00005

nique by indication of the presence of a tone for 100% of the presentations. The step size was 2 programming units. Evaluation of C levels was made by means of either of 2 methods. If a patient had measurable middle ear muscle reflexes with stimulation from the cochlear implant, the level at which the reflex threshold was obtained was used for the maximum C level setting. However, if no reflexes were obtained, C levels were established by means of the scaling procedure for indication of loudness. The maximum C levels were established at the level found to be just below the point of uncomfortable loudness. Although T and C levels might have been set by 1 of 4 audiologists, standard procedures were followed in all programming sessions.

RESULTS

The mean stimulation levels at T for individual electrodes at each test interval are shown in the Figure, A. The Figure clearly illustrates that T levels increased over time. The raw data were analyzed for statistical significance with a repeated-measures analysis of variance. Although the T levels consistently showed an increase at each test interval, the changes were not significant. However, when changes from initial stimulation to most recent programming were analyzed, the changes were significant on 14 of the 20 electrodes ($p < .05$). To account for expected changes in early programs, a comparison of 6-month programming to most recent programming was made, and the difference was found to be significant on 12 of the 20 electrodes.

The mean stimulation levels at C for individual electrodes at each test interval are shown in the Figure, B. Again, the Figure shows an increase in stimulation required to reach C over time. As with T levels, changes

from one interval to the next were generally not significant. When an analysis of the change from the initial stimulation to the most recent evaluation was made, the differences were significant on 19 of the 20 electrodes; however, for the change from 6 months to the most recent evaluation, significance was only reached on 11 of 20 electrodes ($p < .05$).

Table 2 shows the mean stimulation levels and the significance levels of the differences between T and C levels for averaged basal, medial, and apical channels measured at 6 months and the most recent evaluation. Changes in the medial and apical regions were significant ($p < .05$) and appeared to be fairly equal across the array, despite the lack of significance in the apical region.

No significant relationship between length of use and degree of change from the 6-month to the most recent program for the T and C levels was noted; however, of the 5 individuals with more than 5 years of experience, 3 exhibited the greatest degree of change among the group. Additionally, a significant relationship between cause of deafness and degree of change at these intervals was not found.

DISCUSSION

Statistically significant increases in stimulation requirements occurred over time for both T and C levels. Changes from one test interval to the next were not significant. However, the differences between initial stimulation and beyond 1 year were consistently significant across the array. What is not clear is the degree to which the minimal changes seen at 3-month programming intervals affect speech perception and whether statistical significance is equivalent to clinical significance. From the results of this study, it would be difficult to recommend a steadfast interval for programming. Continued monitoring of the changes in stimulation levels or a more discrete analysis of the changes for smaller increments of time is necessary to make such a recommendation. Finally, because this group of subjects has a mean length of implant use of only 3.5 years, it is important to evaluate changes that occur over longer periods in order to better understand the implications of a lifetime of implant use.

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PREDICTING SPEECH PERCEPTION BENEFIT FROM LOUDNESS GROWTH MEASURES AND OTHER MAP CHARACTERISTICS OF THE NUCLEUS 22 IMPLANT

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INTRODUCTION

Programming of the Nucleus 22-channel implant includes obtaining threshold and maximum comfort levels for each individual electrode to be used in the processor map. This process is crucial to speech perception, in that it allows the speech signal to be presented to the user at a level that is audible yet comfortable. The Nucleus 22 implant codes frequency by the place of stimulation along the length of the cochlear duct, and intensity by the amount of current applied to individual electrodes. The clinician can manipulate, to some extent, the electrical dynamic range that the acoustic signal will be mapped onto, as well as the electrodes assigned to cover specific frequency ranges.

Obtaining the threshold and maximum comfort levels across individual electrodes used in the map typically requires that the implant user scale the perceived loudness of a signal that is increasing in electrical current. This process is crucial for enabling the listener to accurately perceive changing intensities of the speech signal, which contribute to the understanding of speech. However, loudness judgments are sometimes difficult to obtain, especially in children. It is hypothesized that the implant user's ability to perceive speech is associated not only with the range of frequencies and intensities represented on the map, but also with the growth of perceived loudness for incoming acoustic stimuli. The importance of loudness growth to speech perception by adults is reflected in data reported by Skinner et al.¹ This study suggests that obtaining consistent growth of loudness is just as important for optimizing speech perception in children.

SUBJECTS AND METHODS

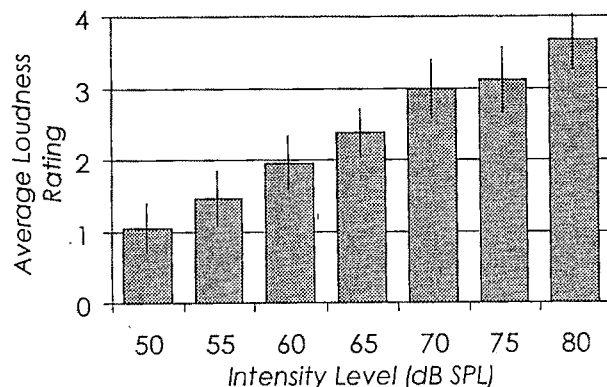
Forty-six 8- and 9-year-olds who all had been implanted before 5 years of age participated in this study. The duration of implant use ranged from 3.98 to 6.94 years (average, 5.5 years). All children initially used an MSP processor programmed with the multipeak (MPEAK) coding strategy. Thirty-six of the children had switched to a SPECTRA processor programmed with the spectral peak (SPEAK) coding strategy. The duration of SPECTRA use ranged from 0 to 36 months (average, 24 months). Twenty-four of the 46 children made use of 20 or more active

electrodes in their map. Twenty children used between 14 and 19 electrodes, and 2 children had maps with only 7 active electrodes.

Several characteristics of the map were obtained from each child's speech processor on the day of testing. These included the number of active electrodes, the dynamic range between the processor threshold and the maximum comfort levels averaged across all active electrodes, and the highest frequency coded. Each child's perceived loudness growth for sound through the speech processor was measured by administering a loudness scaling task. Three different sets of recorded 4-talker babble stimuli were used: 1) a broadband signal, 2) a two-thirds-octave band signal centered at 500 Hz, and 3) a two-thirds-octave band signal centered at 2,000 Hz. All 3 stimuli were calibrated and presented in the sound field in 5-dB increments at levels ranging from 50 to 80 dB sound pressure level. Each intensity level was presented a total of 3 times for each stimulus in a randomized order. Picture stimuli were developed that allowed the children to rate perceived loudness on a 5-point scale: nothing (0), very soft (1), soft (2), perfect (3), and big (4). These responses were averaged across the 3 types of stimuli for the 3 presentations at each intensity level. The graph presented in the Figure shows the average loudness rating at each intensity level for the group of 46 children.

The differences between ratings at each of the 8 adjacent intensity levels were averaged to provide a "loudness growth" score. The average loudness growth score for all subjects using all 3 stimuli was 0.44. This indicated that each increasing intensity level was perceived as approximately one half rating scale point higher than the preceding level. A "variability" score was also obtained for each individual. This score is the standard deviation of the 9 ratings obtained at each intensity level (3 presentations of 3 different stimulus types). The variability score summarized how consistent the child was in judging loudness. The group of 46 children was generally consistent in the rating of loudness, with most subjects varying by no more than 1 rating scale point (average variability, 0.64). The relationship between the perceived growth of loudness and the variability of response was quite strong ($r = .80$). That is, the inconsistency of response decreased with increased perception of the difference between loudness categories.

Speech perception ability was assessed with the Word Intelligibility by Picture Identification test (WIPI).² The WIPI was administered to all subjects by way of recorded



Mean loudness rating is plotted for each intensity level averaged across 3 types of stimuli. Error bars represent standard deviation of response at each intensity level.

TABLE 1. CORRELATIONS WITH SPEECH PERCEPTION SCORES (WIPI)

	<i>r</i>	<i>p</i>
Loudness scaling variables		
Loudness growth score	.49	<.001
Variability score	-.63	<.0001
Map characteristics		
Number of active electrodes	.34	<.02
Average dynamic range	.34	<.02
Highest frequency coded	.45	<.002

WIPI — Word Intelligibility by Picture Identification.²

TABLE 2. CORRELATIONS OF LOUDNESS SCALING VARIABLES WITH MAP CHARACTERISTICS

	Loudness Growth	Variability Score
Number of active electrodes	.51 ($p < .0002$)	-.35 ($p < .02$)
Average dynamic range	.21 (NS)	-.21 (NS)
Highest frequency coded	.21 (NS)	-.21 (NS)

NS — not significant.

stimuli at 70 dB sound pressure level in the sound field, at 0° azimuth. The scores ranged from 0% to 92% correct, with an average score of 47% correct.

RESULTS

The relationships between the children's speech perception score and their map characteristics and performance on the loudness scaling tasks are summarized in the correlation matrix presented in Table 1.² All correlations reached significance, but the highest correlations were obtained on the loudness scaling variables. The greater the ability to perceive differences between loudness categories and the smaller the variability in judgments, the higher the child's speech perception score.

The relationships between the map characteristics and the loudness growth measures are given in Table 2. Although the loudness growth measures were significantly correlated with the number of active electrodes (ie, more active electrodes were associated with greater growth of loudness and more consistent loudness judgments), they failed to correlate with the average dynamic range and the highest frequency coded.

A regression analysis was performed to examine the variance in speech perception scores accounted for by all

of the map characteristics and loudness scaling measures combined. The multiple r was .77, indicating that 60% of the variance in speech perception scores was explained by a combination of these factors. The most variance (32%) was predicted by variability in loudness growth judgments. The highest frequency coded and the average dynamic range also contributed significant additional variance (17% and 11%, respectively). The contribution of the highest frequency coded probably reflected an advantage of SPECTRA users over MSP users.

CONCLUSIONS

These correlations indicate that the better the growth of loudness across the intensity scale and the greater the frequency and dynamic range available, the better the perception of speech. Reports from various sources^{1,3,4} support the importance of optimizing the user's map for intensity and frequency information. This study emphasizes that consistent loudness judgments across the intensity range must be obtained from children to ensure that their ability to perceive speech is maximized with their device.

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SIMULTANEOUS ANALOG STIMULATION PILOT PEDIATRIC STUDY

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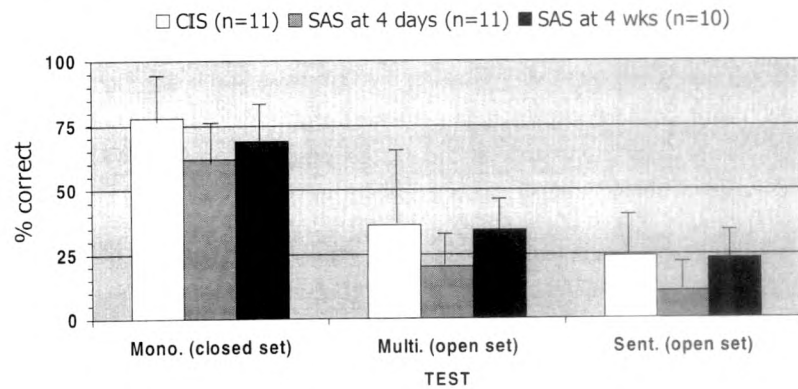
INTRODUCTION

It is well known that children implanted with a CLARION® Multi-Strategy™ Cochlear Implant (Advanced Bionics, Sylmar, Calif) benefit from the monopolar Continuous Interleaved Sampler (CIS) speech processing strategy.¹ The objectives of this pilot study were to determine 1) whether young children can also benefit from the bipolar Simultaneous Analog Stimulation (SAS) speech processing strategy and 2) which factors influence strategy preference.

Over the last year, a number of clinics have investigated the subjective strategy preference and speech understanding of adults fitted with both the Clarion CIS and SAS speech processing strategies.^{2,3} At the Medical University of Hannover (MHH), adults were fitted with CIS

and SAS at the first fitting and monitored for 3 months. The main findings were that 1) 20 of the 22 subjects could be fitted with SAS; 2) 10 of these 20 preferred SAS; 3) the preference did not change over time; and 4) the choice of both CIS and SAS increased overall group performance in speech understanding compared with that in a group given only CIS. The psychophysical data showed that the SAS preference group had lower threshold (T) and most comfortable loudness (M) levels. Another preference study found that one third of patients prefer SAS and, again, that access to a preferred strategy improved overall performance compared with that in subjects given only CIS.³ A more recent crossover study supports these findings, showing that 40% of subjects preferred SAS (J. E. Goldring et al, unpublished observations). In light of the encouraging results in adults with SAS, a pilot study was

Speech perception as measured by monosyllabic (closed-set), multisyllabic (open-set), and sentence (open-set) test results of group preferring Simultaneous Analog Stimulation (SAS). Results are shown with original Continuous Interleaved Sampler (CIS) program (mean experience, 1.6 years), with SAS after 4 days, and with SAS after about 4 weeks. There was no significant difference between CIS and 4-week SAS scores (Wilcoxon, $p < .05$).



completed to determine whether young children could also benefit from SAS. This study comprised 22 children switched from CIS to SAS.

METHODS

Subject Group. Inclusion criteria consisted of all available children over the age of 4 at the Cochlear Implant Center (CIC). Twenty-two children ages 4 to 13 years (mean, 8.4 ± 2.5) entered the study. All were fitted with implants at MHH between May 1995 and June 1997 and were originally fitted at CIC with only CIS (CIS experience ranging from 11 months to 2.3 years; mean, 1.7 ± 0.6 years).

Rehabilitation and Evaluation. The children were fitted with the SAS program on day 1 of a 5-day rehabilitation visit to CIC. The CIS program was removed from the speech processor at the same time. At the end of the week, the children were sent home for 4 to 6 weeks with SAS only. Rehabilitation consisted of daily refittings as needed, training with the therapists, and a variety of play activities. Speech recognition performance was evaluated with parts of the Hannover hearing test, consisting of 1 closed-set test (monosyllabic words) and 2 open-set tests (multisyllabic words and sentences). The children were tested with their most recent CIS programs on day 1 of the rehabilitation week and using SAS on day 5, as well as about 4 weeks later. The children were asked which strategy they preferred (ie, which strategy they liked using more). Additionally, the parents and fitting audiologist filled out a questionnaire.

RESULTS

Fitting. The audiologist reported that the SAS fitting was as easy as the CIS fitting. As with adults, SAS T levels were not used. The T levels add compression in SAS, and most patients do not like the effect. The input dynamic range, an adjustable parameter that determines what range of the acoustic input signal is mapped into the electrical output range, was not adjusted. Some children reported more background noise with SAS than with CIS; however, it was felt that this impression of more noise was the result of hearing more in general and that they would adapt to this increase in noise over time, which they did.

Preference. The 22 children could be split into 3 groups. Group 1 consisted of 6 children who could not be fitted with SAS. Five of these children had CIS or SAS M levels that were too high, and 1 child could not report reli-

able levels. Group 2 consisted of 5 children who rejected SAS (SAS experience varying between hours and 4 weeks). Three rejected SAS as a matter of preference, 1 because of a need to take a test in school and 1 because of skeptical parents and a low frustration level. Group 3 consisted of 11 children who preferred and stayed with SAS.

Psychophysical Data. The Clarion fitting program records T and M current levels in clinical units (CUs), which are a nominal reference to microamperes. The T and M levels from the original CIS program were compared for all 3 groups. Although the levels were similar for groups 2 and 3 (<375 CUs), group 3 had lower levels on all 8 electrodes; the mean difference was 17.4 CUs for T, and 32.5 CUs for M. The SAS users (group 3) had significantly lower T and M levels compared to the entire CIS user group (groups 1 and 2; Wilcoxon $p < .05$).

Speech Tests and Questionnaire. The SAS users showed a degradation in speech recognition after 4 days with SAS, compared to their most recent CIS results. After about 4 weeks of SAS use, however, the mean SAS scores for all 3 speech tests were not significantly different (Wilcoxon, $p < .05$) from the CIS results (see Figure). The children's comments about SAS, as compared to CIS, at the first fitting included that it was strange, was more pleasant, gave more background noise, gave more information, needed getting used to, and was softer. Subjective comments from the parents (and teachers) about those children who chose SAS included that it improved the ability to hear music, improved speech understanding, increased the attention span, enabled a better spontaneous response to speech, improved pronunciation, enabled the child to hear sounds and phonemes never heard before, and enabled the child to hear more background noise.

DISCUSSION

The purpose of this study was to switch children from the CIS strategy to an SAS strategy and determine whether they could benefit from the new strategy. The results demonstrate that SAS was a viable speech processing option for at least half of the children in this study. The fitting was as easy as with CIS. In total, 22 children between 4 and 13 years old took part in the study. Sixteen could be fitted with SAS, and of those 16, 11 preferred and stayed with SAS. Compared with the adult pilot study in which 20 of the 22 subjects were able to be fitted with SAS, it seems that fewer children were able to be fitted with SAS.

This is perhaps because children tend to have higher T and M levels than adults; in this study, those with very high levels were excluded from SAS fitting, while in the adult study, all were fitted with SAS unless levels exceeded the program limit. Earlier studies showed that only 33% to 50% of adults fitted with both strategies preferred SAS, while almost 70% of the children preferred SAS. This suggests that children have the better ability to adapt. With greater parental and teacher support, or with SAS at the first fitting, the number of children choosing SAS might have been even larger. In general, all the children fitted with SAS had T and M levels not exceeding about 375 CUs. The group preferring SAS tended to have lower T and M levels than those preferring CIS, as found in the adult study. One of the most interesting findings was that this group preferring SAS did, on average, as well with SAS after only 4 weeks as with the initial CIS program, where the mean CIS experience was 1.6 years. There were, however, 2 children who subjectively preferred SAS but objectively performed worse with SAS after 4 weeks. Because of the positive findings of this pilot study, an extended multicenter SAS-CIS comparison pediatric study will be conducted in Europe and North America. Two groups of children will be matched on critical demographic information; 1 group will receive CIS, the other SAS. The purpose of this study is to compare the performance of

the 2 processing strategies.

Factors Influencing Preference. The preliminary results suggest that M levels below about 375 CUs in CIS are an indication for fitting SAS. For switching children from CIS to SAS, the factors influencing preference may be M levels with CIS, subject reliability in reporting loudness levels, frustration threshold and adaptive ability, and the concerns and attitudes of the parents and teachers. Although these factors may affect strategy preference, other factors, such as nerve survival, are probably also influencing choice. Future studies will need to focus on the relationships between patient characteristics and strategy preference.

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USING BEHAVIORAL DATA TO MODEL OPEN-SET WORD RECOGNITION AND LEXICAL ORGANIZATION BY PEDIATRIC COCHLEAR IMPLANT USERS

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INTRODUCTION

Children who acquire language through a cochlear implant (CI) provide a unique opportunity to study the physical and cognitive bases of speech perception, as the target language these children must acquire is the same as for children without hearing loss, but the input to the nervous system from a CI is very different from normal hearing. Psycholinguistic models of speech perception in adults with normal hearing propose that the phonological lexicon is organized in a phonetic similarity space based on linguistic features and phonemes, and that these units are important for spoken word recognition. Although the physical signal received through a CI is different from aurally perceived speech, we propose that the same abstract units of language are nonetheless a part of the linguistic knowledge of children who learn spoken language through CIs.

In this paper, we model performance by children with CIs on tests of open-set word recognition using their performance on closed-set tests of feature identification. Our model of word recognition does not employ any free pa-

rameters, and therefore is highly constrained. Modeling the cognitive process of spoken word recognition on the basis of feature identification performance is important to both theoretical and clinical research. The model of word recognition we propose is appropriate for both listeners who use CIs and those with normal hearing. It is therefore a theoretical model of the process of spoken word recognition in general, as well one way to address the question of whether the cognitive process of spoken word recognition is the same for both CI users and those with normal hearing. Comparing observed and predicted open-set word recognition performance from closed-set identification tasks may be particularly useful clinically for the pediatric CI population. If differences between observed and predicted performance can be attributed to particular components of the model, then it may be possible to provide intervention that is maximally beneficial to the child.

MODEL OF OPEN-SET WORD RECOGNITION

Our simulations used data from the pediatric CI user population seen at the Indiana University School of Medi-

cine. In this population, feature identification performance is routinely assessed with the Minimal Pairs Test.¹ In this test, the participant is shown 2 pictures that are associated with words that differ on 1 phoneme (eg, *bear* and *pear*). The difference in phonemes for each item in the test is a difference in 1 dimension of phonological contrast (eg, manner of articulation). Three different dimensions of contrast are tested for consonants (place, manner, and voicing), and 2 different dimensions of contrast are tested for vowels (vowel place and vowel height). If a particular dimension of contrast is not identifiable for a participant, specific predictions about that listener's performance in word recognition can be made. For example, if manner of articulation cannot be reliably identified, then /b/, /v/, and /m/ are predicted to be confusable, as are /p/ and /f/, /t/ and /s/, and so forth.

Performance on feature identification in the Minimal Pairs Test is used to generate predicted phoneme confusion matrices. First, closed-set feature identification performance is converted to predicted open-set feature identification performance by adjusting for the difference in base rate associated with a closed-set task. For a 2-alternative test like the Minimal Pairs Test, the equation is Estimated open-set = $2 \times (\text{observed closed-set} - 50\%)$. Second, we generate confusion matrices for each dimension of contrast by determining which phonemes are no longer distinct when a dimension of contrast is removed. Third, we combine these confusion matrices depending on how reliably the dimensions of contrast are identified by a particular listener. The confusion matrix for each dimension of contrast in the combination is weighted by the listener's performance on the Minimal Pairs Test for that dimension. The weighted confusion matrices are added to create an overall predicted confusion matrix for each listener.

The predicted confusion matrix is applied to the string of phonemes in the target word (eg, a stimulus item on a test of open-set word recognition) to produce a response phoneme string based on that participant's feature identification abilities. The response phoneme string is compared with the words in an on-line dictionary, and the best matching lexical item is selected. For example, if the target word is "cat" /kat/, the model might respond "cat," or it could respond "bat," "dat," "cap," "guk," or any of a number of other responses. Of the responses listed, "cat," "bat," and "cap" are words in the English language, whereas "dat" and "guk" are nonsense syllables.

To simulate open-set spoken word recognition, the phoneme confusion matrix is applied to each phoneme in each word of an open-set word recognition test. A model of word recognition that goes no further, ie, that assumes that a word is recognized as the sum of its phonemes, will be referred to as the Phoneme Confusion Model, or PCM.² A model of spoken word recognition that is psychologically more plausible than PCM includes an additional step in which the mental lexicon is searched for a match to the target word. We use a simple procedure for lexical access that finds the word in the lexicon with the greatest number of phonemes matching the target word. Overlap is

determined on the basis of the optimal alignment of syllabic positions between 2 words. For example, the words *hello* and *heavy* are best aligned at their beginnings, and they overlap in the 2 phonemes /h/ and /E/. The words *hello* and *low* are best aligned by matching the second syllable of *hello* with *low*. Again, they overlap by 2 phonemes, in this case /l/ and /o/. If 2 words tie for the greatest number of matching phonemes, the tie is broken by choosing the word with the highest usage frequency. The model of word recognition that includes lexical access is referred to as Syllable Position Alignment for Matching and Retrieval, or SPAMR.

The SPAMR model uses a simulation of a child's mental lexicon containing a subset of words from an on-line version of a Webster's pocket dictionary that is an approximation of an adult's mental lexicon.³ The simulated child's lexicon was generated with high-frequency words from the adult lexicon, plus all of the words on the 2 tests of open-set word recognition used in these simulations, the Lexical Neighborhood Test (LNT)⁴ and the Phonetically Balanced-Kindergarten test (PBK).⁵ Therefore, we assume all of the words on the word recognition tests are known by the children. It has been claimed that many of the words on the PBK are unfamiliar to young children, so the previous assumption may be incorrect.⁴ The simulated child's lexicon contained about 1,400 words.

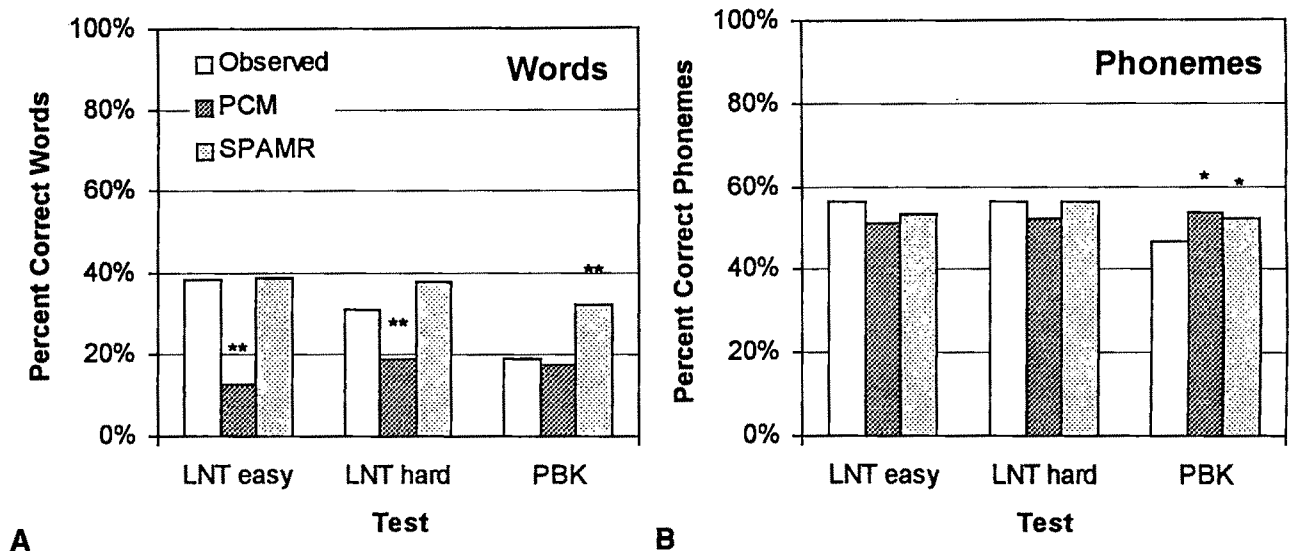
DATA

Behavioral data from 30 pediatric CI users with Nucleus 22-channel CIs and either the spectral peak (SPEAK)⁶ or multipeak (MPEAK)⁷ processing strategies were used. The test scores were obtained 1.5 to 2.0 years after implantation. There were 18 children who used MPEAK and 12 children who used SPEAK. The children had a mean age at onset of profound hearing loss of 0.32 years (median, 0) and a mean age at implantation of 4.45 years (median, 4.60). The children were evenly divided between those who use mainly oral communication and those who use total communication, a combination of spoken and manual communication. Because the data set was relatively small and in the present study we examined only averaged data, the data for the children using the different processing strategies as well as different modes of communication (oral and total communication) were analyzed together.

Our simulations used observed data and simulated recognition of the words in the Minimal Pairs Test, the LNT, and the PBK. The LNT contains 2 sets of stimuli, called "easy" and "hard" on the basis of their confusability with other words in the lexicon. "Easy" words are high-usage frequency words that are similar to only a few other words, which are of low usage frequency. "Hard" words are low-usage frequency words that are similar to many high-usage frequency words. The stimuli on the PBK vary greatly in their lexical characteristics, because the PBK lists were balanced for their phonemic, not lexical, properties.

RESULTS

A comparison of observed and predicted performance



Observed and predicted performance for Lexical Neighborhood Test (LNT) easy words, LNT hard words, and Phonetically Balanced-Kindergarten (PBK) words. PCM — Phoneme Confusion Model, SPAMR — Syllable Position Alignment for Matching and Retrieval. A) Performance scored in percent words correct. B) Performance scored in percent phonemes correct. Significant differences between observed and predicted performances on paired *t*-tests are indicated for models: * — $p < .05$; ** — $p < .01$.

averaged across all the children is given in the Figure. The observed and predicted performances are shown for the LNT easy and hard words separately. First, note that the model with a lexical access component (SPAMR) makes a very good prediction of observed performance in words correct on both easy and hard words on the LNT. The SPAMR model predicts performance in words correct much better than does the PCM. The difference between PCM and SPAMR is greatest for the LNT easy words. These are words that are in sparse neighborhoods of the mental lexicon, so lexical knowledge can be used to "fill in" incomplete acoustic phonetic information. For the PBK, the model with lexical knowledge performed significantly better than the observed level, whereas the model with no lexicon was more accurate. This pattern supports the claim that young children are unfamiliar with many of the words on the PBK.⁴ Because predictions for words correct on the LNT improved with the addition of a stage of lexical access, we believe modeling lexical access is a necessary part of modeling open-set spoken word recognition with these pediatric CI users.

Comparing observed and predicted performance in phonemes correct shows that both PCM and SPAMR make predictions that are very close to observed performance, only overpredicting for the PBK. On the basis of the good predictions for phonemes correct, we conclude that closed-set feature identification can successfully predict phoneme identification in an open-set word recognition task.

CONCLUSIONS

We have demonstrated significant progress in predicting open-set word recognition performance from closed-set feature identification performance in children who use CIs. Different aspects of the model account for phoneme identification and lexical access in word recognition. Comparing observed and predicted open-set word recognition performance may be useful clinically, because closed-set

tests have a more straightforward response format and therefore may be more developmentally appropriate for very young children. However, the psycholinguistic model contains no mechanisms (apart from the choice of a lexicon) specific to children who use CIs. Therefore this model may be useful for other clinical populations, including children and adults with normal hearing. The model will also be used to predict performance for individual CI users who employ different modes of communication. The generality of the model provides evidence that the process of spoken word recognition by children with CIs reflects units of linguistic structure and lexical organization similar to those evident in the process of spoken word recognition by adults with normal hearing.

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COMPARISON OF CHILDREN'S FAMILIARITY WITH TOKENS ON THE PBK, LNT, AND MLNT.

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INTRODUCTION

Open-set word recognition by children with cochlear implants is often assessed with the Phonetically Balanced-Kindergarten (PBK) word lists.¹ However, many children tested with this measure demonstrate relatively modest word recognition abilities.²⁻⁵ It may be that the constraints of phonetic balancing yielded PBK stimuli that were unfamiliar to profoundly deaf children, who often have restricted vocabularies. At Indiana University, 2 new open-set speech perception measures, the Lexical Neighborhood Test (LNT) and the Multisyllabic Lexical Neighborhood Test (MLNT), have been developed to assess spoken word recognition by children with hearing impairment. Stimuli on the LNT and MLNT were selected from the CHILDES⁶ data base, which contains transcripts of verbal exchanges between young children with normal hearing and their caregivers or other children. The LNT and MLNT tokens were selected from the subset of words produced by children ages 3 to 5 years and are therefore assumed to be among the earliest acquired vocabulary. Further, the lexical characteristics of these word lists are controlled in order to obtain information about the way in which children with cochlear implants organize and access words from memory. Previous research demonstrated that the LNT and MLNT yield significantly higher word recognition scores than the PBK in children with cochlear implants.⁷

The purpose of the present investigation was to compare the pediatric cochlear implant users' familiarity with stimuli on the 3 measures. A secondary aim was to examine the relationship between the familiarity of the stimuli and the children's chronological age.

METHODS

Participants in this investigation were selected from the pool of parents whose children participate in our longitudinal study concerning the benefits of cochlear implant use. Parents of children with prelingual profound deafness (age at onset of ≤ 3.0 years) who were implanted before the age of 6 years were invited to participate ($N = 49$ children). The parents of 21 children with the Nucleus 22-channel cochlear implant agreed to complete the word familiarity scale. The average age at implantation was 3.1 years (SD, 1.2 years), and the mean length of device use was 4.2 years (SD, 2.5 years). At the time of this study, the ages of the children ranged from 2.7 to 8.5 years, with a mean of 5.2 years. All participants used the SPECTRA processor with the spectral peak (SPEAK) coding strategy. Thirteen of the children used oral communication, and 8 used total communication.

A 298-item rating scale was used to assess the children's

familiarity with stimuli from the 3 open-set word recognition measures. All the words on the LNT (2 lists of 50 monosyllabic words) and the MLNT (2 lists of 24 multisyllabic words) were included in this scale. However, only 3 of the 4 PBK word lists (50 monosyllabic words per list) were included on the word familiarity rating scale, because previous research has shown that one list differed in difficulty from the other 3 lists.^{1,8} On each LNT and MLNT list, half of the words are lexically easy (ie, they occur often in the language and have few phonemically similar words with which they can be confused), and half are lexically hard (ie, they occur less often and have many phonemically similar words with which they can be confused).

The word familiarity rating scale was mailed to the parent participants. One parent (the primary caregiver, usually the mother) was instructed to rate each child's familiarity with the tokens on the PBK, LNT, and MLNT using a 7-point rating scale (eg, 1 = very unfamiliar; 7 = very familiar). The mean familiarity score was determined across the 3 lists of the PBK. For the LNT and MLNT measures, mean familiarity scores were calculated separately for the easy and hard words within each test. The data were subjected to a 1-way repeated-measures analysis of variance to examine differences in word familiarity ratings between the LNT-Easy, LNT-Hard, MLNT-Easy, MLNT-Hard, and PBK word lists. Also, separate *t*-tests were performed for each word list to compare the familiarity of the words to children who used oral communication versus those who used total communication. Finally, Pearson product moment correlation analyses were used to examine the relationship between word familiarity and chronological age.

RESULTS AND DISCUSSION

Table 1 presents the mean word familiarity ratings obtained for tokens on the LNT, MLNT, and PBK tests. There

TABLE 1. MEAN RATINGS OF WORD FAMILIARITY ACROSS TEST MEASURES

Word Lists	Familiarity Rating (mean $\pm$ SD)
LNT	
Easy words	5.8 $\pm$ 1.6
Hard words	5.6 $\pm$ 1.4
MLNT	
Easy words	5.3 $\pm$ 1.4
Hard words	5.0 $\pm$ 1.5
PBK	4.3 $\pm$ 1.6

1 = very unfamiliar; 7 = very familiar.

LNT — Lexical Neighborhood Test, MLNT — Multisyllabic Lexical Neighborhood Test, PBK — Phonetically Balanced-Kindergarten test.

TABLE 2. CORRELATIONS OF CHRONOLOGICAL AGE WITH SCORES ON WORD FAMILIARITY RATING SCALE

LNT-Easy	.36
LNT-Hard	.40
MLNT-Easy	.46 ($p < .05$)
MLNT-Hard	.49 ($p < .05$)
PBK	.52 ($p < .01$)

was a significant difference in familiarity between words on the LNT, MLNT, and PBK ($p < .0001$). The LNT words were rated as the most familiar, followed by the MLNT and then the PBK words. There were no significant differences in familiarity of the stimuli as a function of lexical difficulty for either the LNT or the MLNT. In addition, within each word list, word familiarity did not differ significantly between children in the oral communication group and those in the total communication group.

Table 2 presents the correlations between the familiarity of the stimulus items on the 3 speech perception measures and the children's chronological age. Word familiarity was significantly correlated with chronological age for the MLNT and PBK, but not for the LNT.

The present results revealed significant differences in the familiarity of words on the LNT, MLNT, and PBK. Of the 3 measures, the words on the PBK were rated as the least familiar to these young children with multichannel cochlear implants. These findings support the notion that poor performance on the PBK may result in part because children with profound hearing loss are not familiar with the test items. The results of the correlational analyses revealed that children's familiarity with stimuli on the PBK and MLNT increases significantly as they age. This was not true for the LNT stimuli. The average word familiarity rating for stimuli on the LNT was ≥ 6 (maximum, 7) for the majority of participants, regardless of

their chronological age. Thus, the LNT words are highly familiar, even to young children with profound deafness. Finally, the results demonstrated that children's familiarity with items on the LNT and MLNT did not differ as a function of lexical difficulty. This suggests that lexical effects on word recognition previously demonstrated with these measures⁷ are independent from the familiarity of the stimulus items. These findings add to the growing body of evidence showing the important role of the lexicon in speech perception and production and in language development.

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RECOGNITION OF MONOSYLLABIC WORDS BY COCHLEAR IMPLANT PATIENTS AND BY NORMAL-HEARING SUBJECTS LISTENING TO WORDS PROCESSED THROUGH COCHLEAR IMPLANT SIGNAL PROCESSING STRATEGIES

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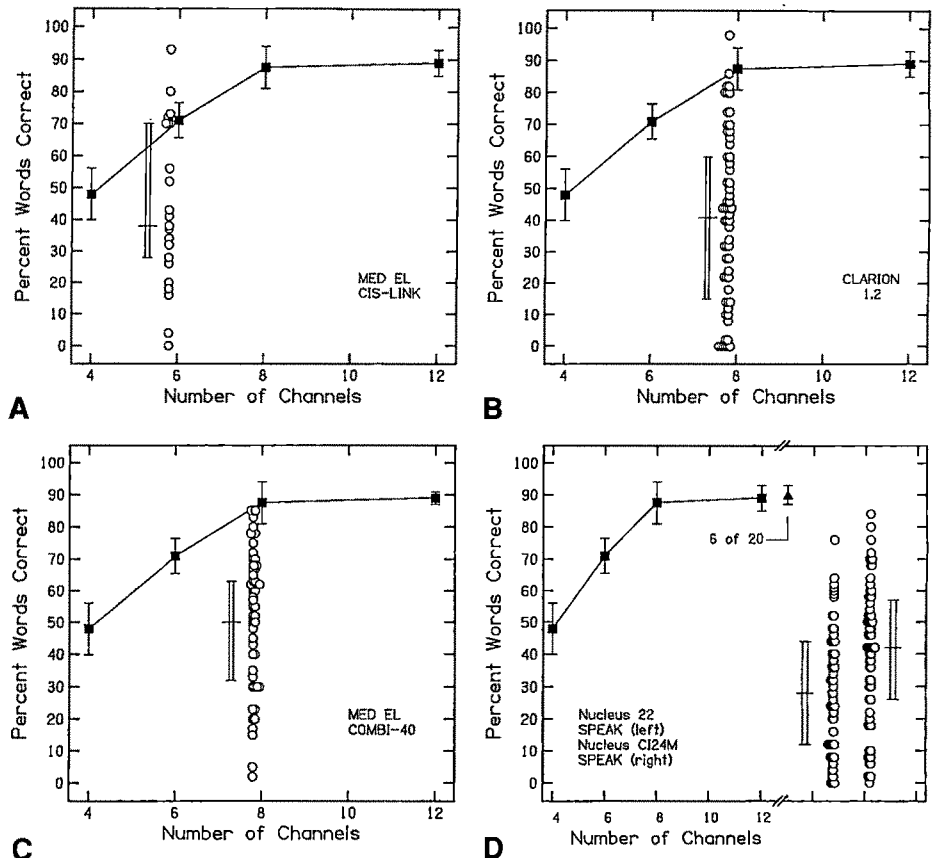
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INTRODUCTION

The aim of a cochlear implant is to generate, by means of artificial electrical stimulation, a pattern of neural activity that conveys to a patient the information in speech signals, music, or environmental sounds. Given recent advances in signal processing and in electrode design, it is appropriate to ask how well the current generation of implants achieves the goal of transmitting the relevant information in the speech signal. One way to answer this

question is to process signals in the manner of a cochlear implant signal processor and present the signals acoustically, by way of noise bands¹ or sine wave stimulation,² to normal-hearing listeners. The performance of the normal-hearing listeners establishes a benchmark for how well implant recipients could perform *if* electrode arrays were able to reproduce, by means of artificial electrical stimulation, the stimulation produced by auditory stimulation of the cochlea, and *if* patients possessed neural struc-

Percent correct word recognition by normal-hearing listeners (solid symbols) and by patients (open circles) fitted with A) Med-El CIS-Link processor, B) Advanced Bionics Clarion 1.2 processor, C) Med-El Combi-40 processor, and D) Cochlear Corporation Nucleus 22 device (on left) and CI24M device (on right). Each open circle represents patient's score. Medians and interquartile ranges of scores for implant patients are indicated by rectangles next to patient data.



tures capable of responding to the electrical stimulation. In this report, we describe the performance of normal-hearing subjects, tested with monosyllabic words processed through fixed-channel, Continuous Interleaved Sampler (CIS)-like signal processing strategies and spectral maximum, spectral peak (SPEAK)-like strategies, and the performance of patients who use cochlear implants with CIS and SPEAK strategies.

METHODS

Subjects. Sixteen normal-hearing listeners were tested with NU-6 words processed through fixed-channel processing algorithms. Nine listeners were tested with words processed in the manner of a SPEAK-like algorithm. The NU-6 scores for 25 patients fitted with the 6-channel Med-El CIS-Link processor were obtained from records at the University of Iowa and the University of Utah. The patients had used their processors for periods ranging from 3 months to 3 years. The scores from 60 patients using the 8-channel Med-El Combi-40 processor were provided by Med-El Corporation. The patients had used their processors for 1 year. The scores of 60 patients using the 8-channel Clarion 1.2 processor were provided by Advanced Bionics Corporation. The patients had used their processors for 6 months. The scores of 59 patients using the Nucleus 22 device and the SPEAK strategy were accumulated from records at the University of Michigan, the House Ear Institute, and the University of Arkansas at Little Rock. The patients had used their processors for periods ranging from 6 months to 2 years. The scores of

66 patients using the Nucleus CI24M device and the SPEAK strategy were provided by Cochlear Corporation. The patients had used their devices for 6 months.

Signal Processing. To produce words for the normal-hearing listeners, signals were first directed to a pre-emphasis filter and then bandpassed into 4-, 6-, 8-, and 12-frequency bands with sixth-order Butterworth filters. The spacing of the frequency bands was logarithmic for the 4-, 6-, and 8-channel processors. For the 12-channel processor, linear spacing of bands was used up to 1 kHz and logarithmic spacing thereafter. The envelope of the signal was extracted by means of full-wave rectification and low-pass filtering at 400 Hz. Sinusoids were generated with amplitudes equal to the root-mean-square (rms) energy of the envelopes (computed every 4 ms) and with frequencies equal to the center frequencies of the bandpass filters.

For the SPEAK-like, or "n of m," strategy, the number of "m" channels was fixed at 20, and every 4 ms, the 2, 4, or 6 "n" channels with the maximum energy were identified and output as sine waves at the center frequency of the filter band.

Procedure. The normal-hearing subjects were tested with 50 words from one of the NU-6 word lists in each channel condition. Practice for each condition consisted of 50 words processed in the manner of that condition. The implant recipients in the United States were tested with one of the 50-word NU-6 lists. The subjects tested in Europe were tested with monosyllabic word lists ap-

propriate for their language. Responses were scored in terms of words and phonemes correct.

RESULTS

The results for the normal-hearing subjects listening to signals processed with fixed-channel strategies are shown as solid squares in each of the 4 panels of the Figure. The mean word scores for processors with 4, 6, 8, and 12 channels were 48% correct, 71% correct, 87% correct, and 89% correct, respectively. The mean phoneme scores were 67% correct, 85% correct, 95% correct, and 96% correct, respectively.

The performance of the 6-channel CIS-Link patients is shown in the Figure, A. Five of the 25 patients achieved scores within or just outside of the standard deviation for the performance of the normal-hearing listeners. The median score was 38% correct, and the interquartile range was 27% to 70% correct.

The performance of the Clarion 1.2 patients is shown in the Figure, B. Seven of the 60 patients achieved scores within or near the standard deviation for the performance of the normal-hearing subjects listening to words processed into 8 channels. The median score was 41% correct, and the interquartile range was 15% to 60% correct.

The performance of the Med-El Combi-40 patients is shown in the Figure, C. Five of the 60 patients achieved scores within or near the standard deviation for the performance of the normal-hearing subjects listening to words processed into 8 channels. The median score was 50% correct, and the interquartile range was 32% to 63% correct.

The mean scores for normal-hearing subjects listening to signals processed by 2-, 4-, and 6-of-20 SPEAK-type processors were 73%, 87%, and 90% correct, respectively. The score for the 6-of-20 strategy, the one most similar to the SPEAK strategy, is shown in the Figure, D, along with the scores for fixed-channel processors and the scores for Nucleus 22 SPEAK patients and CI24M SPEAK patients. None of the Nucleus 22 subjects achieved scores within the standard deviation of scores of normal-hearing subjects listening to either an 8-channel processor or a 6-of-20 processor. The median score was 28% correct, and the interquartile range was 12% to 44% correct. Two of the CI24M patients achieved scores within the standard deviation of scores for normal-hearing subjects listening to an 8-channel processor. The median score was 42% correct, and the interquartile range was 25% to 56% correct.

DISCUSSION

A number of patients using devices with 8 or more channels achieved scores that were within the range of scores achieved by normal-hearing subjects listening to words processed into 8 channels. This outcome is particularly impressive, because the mean score for the normal-hearing listeners — 87% — is at such a high level. However, because the normal-hearing listeners had very limited experience with signals processed into a small number of

channels, the estimate of potential performance may be too conservative. If the performance of normal-hearing listeners improved only a little with extended practice, eg, 10%, then the scores of the best-performing patients, with only 2 exceptions, would fall within the range of performance of normal-hearing subjects listening to signals processed into 6 channels. Given this possibility, we conclude that electrical stimulation of the cochlea is capable of reproducing with high fidelity the acoustic information in 6 to 8 channels.

On the other hand, our results indicate that on average, patients achieve scores within the range of scores achieved by normal-hearing subjects listening to speech processed into 4 channels. This outcome indicates a need for significant improvements in cochlear implants.

It is important to note that the two 8-channel devices employ different electrode arrays, and patients fitted with each of the arrays were able to achieve scores within the range of the normal-hearing listeners. The performance of the 6-channel CIS-Link patients is of interest, in this light, because the 6 monopolar electrodes are spaced 4 mm apart, and the most basal electrodes stimulate a range of frequencies far outside the normal range of frequencies in the speech signal. Cortical recognition routines for speech must be extremely flexible to accommodate the large distortions in the frequency representation of speech engendered by electrical stimulation of the cochlea.

The data reported here for implant patients cannot be used to compare the efficacy of one implant device with that of another. The population samples were not matched for variables, such as length of device use and length of deafness, that are known to affect performance. Another variable, the level of preoperative speech reception, was not controlled and appears to account for the higher mean scores of patients using the Nucleus CI24M compared with those in patients using the Nucleus 22. Rubinstein et al³ report that in the Iowa sample of implant patients, Nucleus 22 patients and CI24M patients fitted with implants in the 1990s had significantly better preimplant speech recognition scores than Nucleus 22 patients fitted with implants in the 1980s. Test scores for the Nucleus 22 patients given their implants later and Nucleus CI24M patients were similar, and both were higher than the scores for the Nucleus 22 patients given their implants earlier. Therefore, the improved scores for the CI24M patients appear to be related to a patient variable — perhaps the number and distribution of spiral ganglion cells — rather than a processor variable.

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RECOGNITION OF SENTENCES IN NOISE BY NORMAL-HEARING LISTENERS USING SIMULATIONS OF SPEAK-TYPE COCHLEAR IMPLANT SIGNAL PROCESSORS

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To assess whether more channels are needed to understand speech in noise than in quiet, we processed speech in a manner similar to that of spectral peak–like cochlear implant processors and presented it at a +2-dB signal-to-noise ratio to normal-hearing listeners for identification. The number of analysis filters varied from 8 to 16, and the number of maximum channel amplitudes selected in each cycle varied from 2 to 16. The results show that more channels are needed to understand speech in noise than in quiet, and that high levels of speech understanding can be achieved with 12 channels. Selecting more than 12 channel amplitudes out of 16 channels did not yield significant improvements in recognition performance.

INTRODUCTION

Previous studies^{1,2} have shown that when speech is processed in the manner of cochlear implants and presented in quiet to normal-hearing listeners, greater than 90% sentence recognition can be achieved with as few as 4 channels of stimulation. In the real world, however, implant patients often need to communicate in noisy environments. At issue is whether more channels are needed in noisy environments to achieve high levels of speech understanding. To gain insight into this issue, we processed speech through a simulation of a spectral peak (SPEAK)–like cochlear implant processor and presented it at a +2-dB signal-to-noise ratio (S/N) to normal-hearing listeners. The total number of channels was varied from 8 to 16. To investigate whether the SPEAK-type implant processors, which select in each cycle a small number of channel outputs from a larger set, offer any advantages in noise, we also varied the number of channels selected from 2 to 16.

METHODS

Subjects. Ten normal-hearing subjects at Arizona State University, ranging in age from 22 to 55 years, participated in the experiment. The subjects were paid for their participation.

Speech Material. Sentences taken from the Hearing In Noise Test (HINT) database³ were used. The sentences were presented at a +2-dB S/N, with spectrally shaped noise computed from the long-term average spectrum of speech. Twenty sentences were used for each test condition. All sentences were stored on computer disk and were output by means of custom software routines using MATLAB software and a 16-bit digital-to-analog converter.

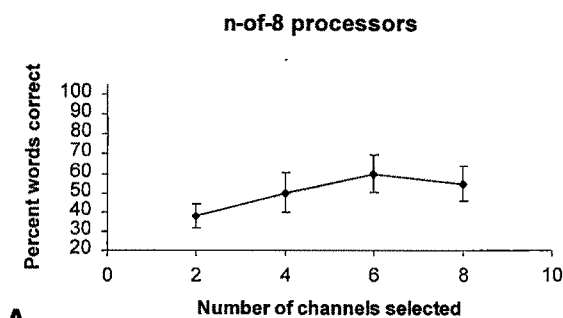
Signal Processing. In SPEAK-type or “n-of-m” processors, the signal is bandpassed into m channels, and the n ($n < m$) channels with the largest energy are selected for stimulation in each cycle. The sentences were processed in a manner similar to a SPEAK cochlear implant processor⁴ to produce 3 types of processors: n-of-8 ($n = 2, 4, 6, 8$), n-of-12 ($n = 2, 4, 6, 8, 12$), and n-of-16 ($n = 2, 4, 6, 8, 12, 16$) processors. The signal was first processed through a pre-emphasis filter (low-pass below 1,200 Hz, 6 dB per octave) and then bandpassed into 8-, 12-, or 16-frequency bands with sixth-order Butterworth filters. Logarithmic spacing was used for the n-of-8 processors, and mel spacing was used for the n-of-12 and n-of-16 processors. The

envelope of the signal was then extracted by means of full-wave rectification and low-pass filtering (second-order Butterworth with a 400-Hz cutoff frequency). Sinusoids were generated with amplitudes equal to the root-mean-square (rms) energy of the n maximum envelopes (computed every 4 ms) and with frequencies equal to the center frequencies of the n selected channels. The n sinusoids were finally summed and presented to normal-hearing listeners for identification through Sennheiser HMD 410 headphones. The number of channels (n) selected varied from 2 to 16, depending on the processor. For the 4-of-12 processor, for example, $n = 4$, and in each cycle, the 4 (of 12) maximum channel outputs with the largest amplitude were selected for stimulation.

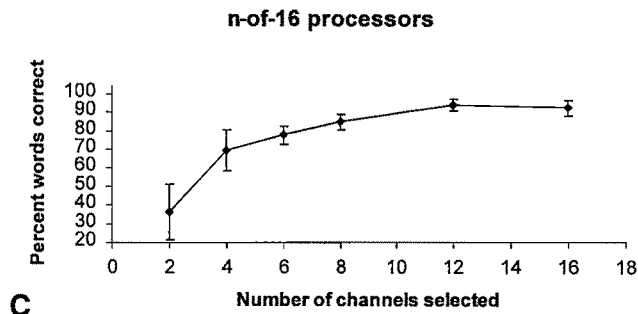
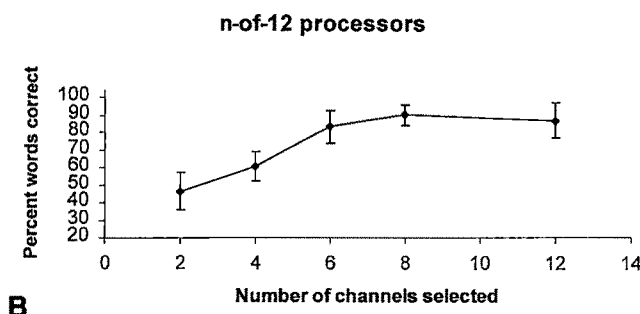
Procedure. The subjects were tested with the n-of-8, n-of-12, and n-of-16 processors and the HINT sentences in a +2-dB S/N. Twenty sentences were used for each test condition. The subjects were presented for practice with 100 Texas Instruments & Massachusetts Institute of Technology sentences processed in a manner similar to each processor condition. The test sentences within each processor condition were all randomized. During the test, the responses were entered with the use of the computer keyboard. The test was self-paced.

RESULTS

The results, in terms of percent words correct, are shown in the Figure. The sentence recognition performance for the n-of-8 processors is shown in the Figure, A. The mean word scores for 2-, 4-, 6-, and 8-of-8 processors were 38%, 50%, 60%, and 55% correct, respectively. Repeated-measures analysis of variance indicated a significant main effect [$F(3,27) = 29.807, p < .0001$] for the number of channels selected out of 8 channels. Post hoc tests showed that the mean word score obtained with the 8-of-8 processor was significantly lower [$t(9) = 2.414, p < .05$] than the mean word score obtained with the 6-of-8 processor. Seven of the 10 listeners showed a decrease in performance from the 8-of-8 processor to the 6-of-8 processor. The sentence recognition performance for the n-of-12 processors is shown in the Figure, B. The mean word scores for 2-, 4-, 6-, 8-, and 12-of-12 processors were 46%, 61%, 83%, 90%, and 87% correct, respectively. Repeated-measures analysis of variance indicated a significant main effect [$F(4,36) = 94.216, p < .0001$] for the number of channels selected out of 12 channels. Finally, the results for



Speech recognition as function of number of channels selected. Error bars indicate ± 1 standard deviation. A) For n-of-8 processors. B) For n-of-12. C) For n-of-16.



the n-of-16 processors are shown in the Figure, C. The mean word scores for 2-, 4-, 6-, 8-, 12-, and 16-of-16 processors were 36%, 69%, 77%, 84%, 94%, and 92% correct, respectively. Repeated-measures analysis of variance indicated a significant main effect [$F(5,45) = 82.997$, $p < .0001$] for the number of channels selected out of 16 channels. Post hoc tests showed no significant difference between the scores obtained with the 12-of-16 processor and the 16-of-16 processor.

DISCUSSION

Our previous studies¹ showed that in quiet, only 4 or 5 channels of stimulation were necessary to achieve greater than 90% accuracy in sentence understanding. The present study shows that this is not the case in noise. At a +2-dB S/N, where performance is not constrained by a ceiling effect, speech understanding improves significantly as more channels are added. Twelve channels were needed to reach maximum performance. Using 16 channels did not produce any significant improvements in sentence understanding compared with the 8-of-12 processor (92% versus 90% correct). The results of this study also show that if a small number (<12) of channels is used, then a SPEAK-like or "n-of-m" processor may offer some advantages in noise compared with a fixed-channel processor (ie, an m-of-m processor). The mean word score obtained with a processor that selected, in each cycle, 6 of 8

channels (6-of-8 processor) was significantly higher than the mean word score obtained with a processor that selected all channels (8-of-8 processor) for stimulation. Seven of the 10 listeners showed a decrease in performance listening to speech processed through an 8-of-8 processor versus a 6-of-8 processor. These results are consistent with those reported by Kendall et al.⁵ Overall, our results suggest that cochlear implant patients may gain more benefit in noise using an n-of-m strategy (eg, such as the one currently implemented in the Med-El Combi-40+ device) rather than a fixed-channel strategy (ie, an m-of-m strategy).

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MODELING PHONEME AND OPEN-SET WORD RECOGNITION BY COCHLEAR IMPLANT USERS: A PRELIMINARY REPORT

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INTRODUCTION

The overall goal of modeling speech perception by cochlear implant (CI) users is to understand the sensory and perceptual mechanisms that CI users employ to understand spoken language. Frisch and Pisoni¹ (also Frisch et al, this supplement, pp 60-62) have developed mathematical models to predict open-set phoneme and word recognition from closed-set feature identification scores for a group of children with profound prelingual hearing losses who use CIs. In the models, individual phonemes are characterized by their various phonetic features. Probabilities of identification of various phonetic features are obtained from vowel and consonant confusion matrices and are used as input parameters to 2 variations of the model. In the first model, candidate responses in an open-set word recognition test are generated by stringing together the most likely phonemes on the basis of feature identification scores. This version, referred to as the Phoneme Confusion Model (PCM),¹ assumes that a word is recognized by identifying each phoneme independently of the others. A model of open-set word recognition that is psychologically more plausible than PCM includes an additional step, in which a lexicon is searched for a possible match to the model output. This model is referred to as Syllable Position Alignment for Matching and Retrieval (SPAMR; this supplement, pp 60-62). The SPAMR model uses an on-line version of a Webster's pocket dictionary² as an approximation of the mental lexicon, and it finds the word in the lexicon with the greatest number of phonemes matching the model output. In the present study, we obtained predictions of open-set spoken word recognition from averaged vowel and consonant confusion matrices from a group of adult CI users.

METHODS

Data. Vowel and consonant confusion matrices³ obtained from 7 adults who were experienced users of the Nucleus 22 CI with the spectral peak (SPEAK) strategy⁴ were used as input to the PCM and SPAMR models. Although the confusion matrices for the individual CI users were available at the time of the study, each CI user heard only 12 repetitions of each stimulus. The average word and phoneme scores on the consonant-nucleus-consonant (CNC) test⁵ for the 7 CI users were compared with the predicted scores from the outputs of the PCM and SPAMR models.

Model. The average vowel and consonant confusion matrices were input to the PCM or SPAMR models, which generate strings of phonemes as possible responses to the stimulus. Given a particular word as input, the models output different strings of phonemes with the proper statistical distribution for the identification of different phoneme features. For example, if the stimulus were the word "seek" /sik/, the model would output /sik/ a certain number of times depending on the feature identification scores. The models might also output "zut," "fak," "seat" /sit/, or "sick" /slk/ as possible responses that are similar to the target word. The PCM model would simply keep track of the number of correct phonemes and words. The SPAMR model, however, would find "seat" /sit/ or "sick" /slk/ in

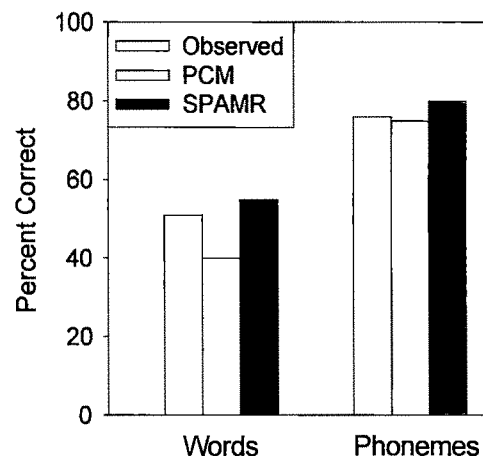
the lexicon, and the number of phonemes would be counted, but it would not find "zut" or "fak." The SPAMR model would search the lexicon for the word or words closest in phonemic structure to "zut" or "fak" and consider these the responses. The numbers of words and phonemes correct were calculated from the model output and compared with the numbers of words and phonemes obtained by the CI users.

RESULTS

A comparison of the average observed and predicted performances on the CNC test is given in the Figure. First, note that the PCM model, which does not use a lexicon, underpredicts the observed performance in words correct. The PCM model predicted only 40% words correct, whereas the listeners actually obtained approximately 51% words correct. The SPAMR model, which includes a lexicon, obtained 55% word identification and 80% phoneme identification, which was quite close to the observed CNC scores for words (51%) and phonemes (76%) correct, and thus provides a better prediction of observed performance than the PCM model. Comparing observed and predicted performance in *phonemes* correct shows that both models make predictions that are very close to observed performance.

SUMMARY

On the basis of the good predictions for phonemes correct, we conclude that closed-set feature identification may successfully predict phoneme identification in an open-set word recognition task. For word recognition, however, the PCM model underpredicted observed performance, and the addition of a mental lexicon (ie, the SPAMR model) was needed for a good match to data averaged across 7 adults with CIs. The predictions for words correct improved with the addition of a lexicon, providing support for the hypothesis that lexical information is used in open-set spoken word recognition by CI users. The perception of words more complex than CNCs is also likely to require lexical knowledge (Frisch et al, this supplement, pp



Observed and predicted performance for CNC words. Percent words correct is shown in left portion of Figure, and percent phonemes correct is shown in right. PCM — Phoneme Confusion Model, SPAMR — Syllable Position Alignment for Matching and Retrieval.

60-62). In the future, we will use the performance of individual CI users on psychophysical tasks to generate predicted vowel and consonant confusion matrices to be used to predict open-set spoken word recognition.^{6,7}

ACKNOWLEDGMENT — We thank Dr Margaret W. Skinner for allowing us access to the vowel and consonant confusion matrices.

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NEW DIRECTIONS IN SPEECH PROCESSING: PATIENT PERFORMANCE WITH SIMULTANEOUS ANALOG STIMULATION

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The CLARION® Multi-Strategy™ Cochlear Implant was designed to offer flexibility in speech processing to accommodate new schemes as they are developed and to offer options to each individual user.¹ The purpose of the present study was to examine patient benefit from 2 radically different speech processing strategies in the Clarion implant. The Simultaneous Analog Stimulation (SAS) strategy employs digitally reconstructed waveforms that stimulate all electrodes simultaneously. In contrast, the Continuous Interleaved Sampler (CIS) strategy is a non-simultaneous scheme that delivers pulsatile waveforms sequentially across the electrodes.

The results of a previous study showed that approximately one third of the patients preferred to use SAS, and two thirds preferred to use CIS.² Significantly higher consonant-nucleus-consonant (CNC) word recognition scores were demonstrated by the SAS users than by the CIS users after 3 months of implant use. Examination of the relationship between patient characteristics, strategy use, and performance revealed that 2 variables were significant and independent predictors of the 3-month CNC word score: the duration of deafness at time of implantation and the preferred strategy.³ That is, patients with a short duration of deafness achieved higher word recognition scores than did patients with a long duration of deafness, and patients with a similar duration of deafness performed better with SAS than with CIS. The present study extends the results of the previous ones by examining performance after 3 and 6 months of implant use. In addition, sentence recognition was assessed in noise at the 6-month interval.

METHODS

The subjects consisted of the first 58 patients enrolled in the study who had been evaluated 3 and 6 months after implantation as of this report. All patients had profound

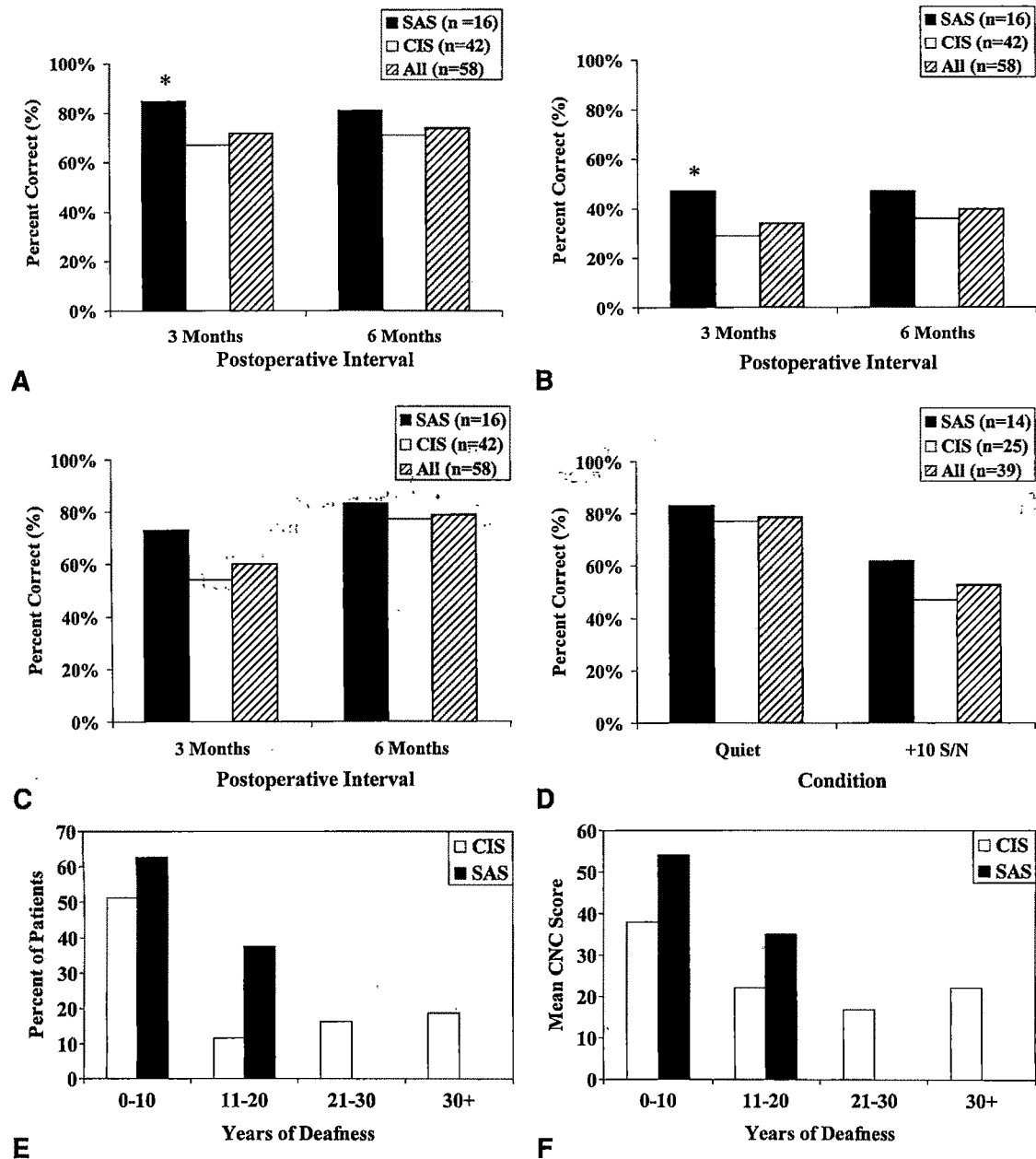
bilateral hearing loss (a pure tone average [PTA] of ≥ 90 dB hearing level [HL]) and a postlingual onset of deafness, and demonstrated negligible hearing aid benefit, defined as a score of $\leq 20\%$ on Central Institute for the Deaf (CID) sentences. The 58 patients demonstrated the following characteristics (mean values): 54 years of age, 13 years' duration of deafness, unaided PTAs of 111 dB HL (implant ear) and 109 dB HL (nonimplant ear), CID score of 4%, and CNC word score of 1%.

Speech recognition performance was evaluated before and after implantation by means of the CID and Hearing In Noise Test (HINT) sentence tests and the CNC monosyllable word test.^{4,5} The HINT sentences (2 lists of 10 sentences) were administered at a fixed level rather than adaptively. The stimuli were presented at 70 dB sound pressure level (SPL) in the sound field. At the 6-month postoperative interval, HINT sentences (2 lists of 10) were administered in the presence of spectrally matched background noise at a +10 signal-to-noise ratio. Before implantation, the measures were administered in the best aided condition. After implantation, the tests were administered while the patients were using their preferred strategies (ie, SAS or CIS) in their Clarion speech processors.

At the time of initial stimulation, the patients were fitted with SAS with bipolar stimulation and CIS with monopolar stimulation. The first 36 patients in the study received the 1.2 speech processor. The next 22 patients received the S-series speech processor, which was introduced after the initiation of the study. The patients were instructed to use each strategy as often as possible in a variety of everyday situations.

RESULTS

At the 3-month postoperative evaluation, all patients had developed a preference for either SAS or CIS. Six-



Test scores of Clarion patients who preferred Simultaneous Analog Stimulation (SAS) and those who preferred Continuous Interleaved Sampler (CIS). A) Scores (percent correct) on CID sentence test for patients who preferred to use SAS (n = 16) or CIS (n = 42) and entire study group at 3- and 6-month postoperative intervals. B) Scores (percent correct) on consonant-nucleus-consonant (CNC) monosyllabic word test for patients who preferred to use SAS (n = 16) or CIS (n = 42) and entire study group at 3- and 6-month postoperative intervals. C) Scores (percent correct) on Hearing In Noise Test (HINT) in quiet (sentence test) for patients who preferred to use SAS (n = 16) or CIS (n = 42) and entire study group at 3- and 6-month postoperative intervals. D) Scores (percent correct) on HINT in quiet and noise (sentence test) for patients who preferred to use SAS (n = 14) or CIS (n = 25) and entire study group at 6-month postoperative interval. S/N — signal-to-noise ratio. E) Distribution (percentage of patients) of SAS (n = 16) and CIS (n = 42) users by duration of deafness (years) at time of implantation. F) Mean CNC word scores (percent correct) after 3 months of implant use for SAS (n = 16) and CIS (n = 42) users by duration of deafness (years).

teen patients, or 28% of the study group, preferred SAS, and 42 patients, or 72% of the group, preferred CIS.

The Figure, A, summarizes the mean scores on the CID sentences after 3 and 6 months of implant use for the SAS and CIS users. At the 3-month interval, the mean score of the SAS users was 85% (SD, 21; median, 95%), which was significantly higher ($t(42) = -2.3$, $p < .05$) than the

mean score of the CIS users (mean, 67%; SD, 35; median, 80%). After 6 months of device use, there was still a trend for higher performance by the SAS users than in the CIS users, but the difference was no longer statistically significant. The 6-month mean score of the SAS users was 81% (SD, 29; median, 94%), compared with a mean score of 71% (SD, 32; median, 87%) for the CIS users. Thus the scores of the SAS users remained relatively un-

changed in the 3-to-6-month interval, whereas the CIS users showed improvement at the 6-month evaluation.

The Figure, B, shows the results for the CNC test. The performance of the SAS users was significantly higher than that of the CIS users at the 3-month interval ($t(23) = -2.4, p < .05$), but not at the 6-month interval. The mean 3-month CNC score of the SAS users was 47% (SD, 25; median, 49%), compared with a mean score of 29% (SD, 21; median, 29%) for the CIS users. At the 6-month evaluation, the mean score of the SAS users was 47% (SD, 25; median, 46%), and the mean score of the CIS users was 36% (SD, 22; median, 36%). Again, the performance of the SAS users remained fairly stable from the 3-month evaluation to the 6-month evaluation, whereas the performance of the CIS users improved.

The Figure, C, shows the results for the HINT sentences in quiet. At the 3-month interval, the mean score of each group of patients was about 10% lower than that demonstrated on the CID sentences (see Figure, A). At the 6-month interval, the performance of both groups of patients improved and was comparable to their 6-month performance on the CID sentences. The mean HINT score for the SAS users was 73% at 3 months (SD, 27; median, 88%) and increased to 83% (SD, 22; median, 90%) at the 6-month interval. The mean score for the CIS users was 54% at 3 months (SD, 34; median, 65%) and increased to 77% (SD, 21; median, 81%) at the 6-month interval. Although there was a trend for better performance by the SAS users than by the CIS users at the 3-month interval, the difference was not significant.

The Figure, D, shows the 6-month results for the HINT sentences in quiet and noise. The mean score of the SAS users in noise was 62% (SD, 25; median, 70%), and the mean score of the CIS users was 47% (SD, 31; median, 42%). The difference in performance between the SAS and CIS users was not statistically significant. Both groups obtained higher scores in quiet than in noise, but the difference between the 2 conditions is larger for the CIS users than for the SAS users. The average difference between the "quiet" scores and "noise" scores for the SAS users was 21%, compared with a mean difference of 30% for the CIS users.

A regression analysis was performed to examine the contributions of duration of deafness and preferred strategy to performance on the CNC word test at the 3-month interval. The results revealed a significant effect of duration of deafness ($p < .001$). Preferred strategy approached, but did not reach, statistical significance ($p = .076$).

A closer examination of the relationship of preferred strategy to duration of deafness is shown in the Figure, E. The distribution of SAS and CIS users by duration of deafness showed that patients with a shorter duration of deafness tended to choose SAS more often. In contrast, patients with a longer duration of deafness always chose to use CIS. The Figure, F, shows the mean 3-month CNC scores of the SAS and CIS users by duration of deafness. There is a trend for SAS users to achieve higher word recognition scores than CIS users with a similar duration of deafness.

DISCUSSION

The results of this study revealed significantly higher performance by the SAS users than by the CIS users on the CNC word and CID sentence tests after 3 months of implant use. At the 6-month interval, the differences between the groups were no longer significant, because the performance of the CIS users had improved, whereas the performance of the SAS users remained fairly stable. This finding suggests that the patients who used SAS demonstrated a faster rate of learning with their strategy than did the CIS users. The implication of this finding is of particular importance for children, in whom faster rates of learning might result in fewer delays in the development of auditory, speech, and language skills.

The contribution of duration of deafness to performance with an implant has been reported by other investigators.⁶⁻⁸ Although early implantation in children is widely accepted, the results of this and previous studies clearly suggest that delayed implantation in adults also has a negative impact on postimplantation benefit. Therefore, adults, as well as children, should be fitted with implants as soon as candidacy has been established.

Although the results of this study showed that duration of deafness primarily accounted for the variance among patients in postimplantation performance, there was a trend for better performance by the SAS users compared with the CIS users with a similar duration of deafness after 3 months of implant use. The strategy preference did not have a significant ($p = .76$) impact on postimplantation performance in this study, presumably because the sample size was smaller than those in our previous investigations.^{2,3}

The percentage of patients who can benefit from a simultaneous strategy may increase with improvements in electrode placement to increase channel selectivity and reduce channel interaction. The CLARION Electrode Positioning System™ (EPS) is designed to enhance the modiolus-hugging properties of the Clarion electrode so that discrete populations of auditory neurons are stimulated. The EPS received approval for commercial distribution in adults in January 2000. The HiFocus Electrode™ with Positioner was introduced in 1999, and is currently under clinical investigation in North America. Initial results with the HiFocus electrode, designed to provide more discrete stimulation and improved channel selectivity, reveal that 90% of adult patients prefer to use either a fully simultaneous speech processing strategy (SAS) or a partially simultaneous strategy (Paired Pulsatile Sampler).

ACKNOWLEDGMENTS — We thank the surgeons and audiologists at the following centers for their efforts in patient management and data collection: Boys Town National Research Hospital, Johns Hopkins University School of Medicine, House Ear Clinic, Midwest Ear Institute, Shea Clinic, Tampa Bay Hearing and Balance Center, University of California at San Francisco, University of North Carolina at Chapel Hill, University of Minnesota, University of Pennsylvania, Warren Otologic Group.

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EARLY EXPERIENCE WITH THE COCHLEAR ESPRIT EAR-LEVEL SPEECH PROCESSOR IN CHILDREN

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The ESPrit ear-level speech processor has recently become available in the United Kingdom for use with the Nucleus CI24M multichannel cochlear implant. We report on the use of this ear-level processor with 6 children, ages 8 to 15 years. In this study, all patients were initially fitted with the SPrint body-worn processor, this being a prerequisite for programming the ESPrit. Five of the children were fitted successfully with the ESPrit and are using their devices consistently. The results show that patient experience with the ESPrit has been favorable, although there have been some device and programming difficulties. Aided threshold measures show that the ESPrit processor performs at least as well as the SPrint processor, with a trend toward improved aided thresholds for the ESPrit processor compared with the SPrint processor. Further study of the functional benefit of both of these devices may confirm these potential gains. The ESPrit device currently has a disadvantage for children in that it does not support FM radio hearing aid use. Finally, caution is advised in the fitting of the ESPrit in very young children or inexperienced listeners, because of difficulties in monitoring device function.

INTRODUCTION

Multichannel cochlear implantation began in the United Kingdom at Nottingham in 1989 with the Nucleus CI22 system. In August 1994, all children in the Nottingham program were upgraded from the Mini Speech Processor to the SPECTRA 22 speech processor. The first Nucleus CI24M systems were implanted in April 1997. All children have since been implanted with the CI24M device and use the SPrint body-worn speech processor at initial stimulation. Six experienced SPrint users have recently been supplied also with ESPrit ear-level speech processors, and in this paper, we present a preliminary report on the early findings and experiences of these children. Older children, from 8 to 15 years, were used in this study, because they had established communication skills and were able to describe their experiences. Comparative data from the ESPrit ear-level processor and the SPrint body-worn processor are presented.

METHODS

Devices. The SPrint is a body-worn speech processor. It has 4 listening programs available for different environments and has the option of 3 processing strategies: spectral peak (SPEAK), Continuous Interleaved Sampler (CIS), and Advanced Combination Encoders (ACE). Only the SPEAK strategy was used for this study. There is an option to have a volume control in addition to a microphone sensitivity control, but only the sensitivity control was available to the children in this study. The ESPrit is a small, lightweight, behind-the-ear speech processor. It has a sensitivity/volume adjustment knob, which was set to the sensitivity option for these children. Two listening programs are available, but currently only 1 speech processing strategy is available (the SPEAK strategy). Both processors have autosensitivity controls that automatically decrease the microphone sensitivity in a noisy environment. This control was not used in this study.

Children. Table 1 shows the salient characteristics of the children studied. Five of the 6 children had postlingually acquired profound deafness. One child acquired profound deafness at 1 year of age and had already been implanted with 2 Nucleus CI22 devices on successive occasions. Both devices had failed, and both had required explantation. The child was subsequently fitted with a CI24M.

Measures Used. We used aided sound field thresholds, measured with warble tone stimuli, speech discrimination, and diaries completed by each of the children, together with comments from parents. Aided sound field warble tone threshold measurements were undertaken with the

TABLE 1. CHARACTERISTICS OF CHILDREN STUDIED

Child	Sex	Age at Implantation (y)	Age at Onset of Profound Deafness (y)	Experience With SPrint (wk)
1	F	8.7	5.3	26
2	M	8.5	8.0	12
3	M	9.9*	1.0	12
4	F	11.5	10.2	12
5	F	14.7	10.9	12
6†	F	9.3	6.7	52

*Reimplanted with CI24M; initially underwent implantation at 4.6 years.

†Map unable to be converted from SPrint to ESPrit processor.

TABLE 2. MEAN AIDED THRESHOLD AND LISTENING LEVEL REQUIRED FOR 71% SPEECH DISCRIMINATION SCORE FOR SPRINT AND ESPRIT PROCESSORS

Measure	SPrint	ESPrIt
500 Hz	35 ± 4	33 ± 5
1,000 Hz	35 ± 4	32 ± 4
2,000 Hz	35 ± 5	30 ± 3
3,000 Hz	33 ± 3	27 ± 3
4,000 Hz	29 ± 3	26 ± 1
Speech discrimination	48 ± 9	46 ± 6

Data are mean ± SD, in dB (A).

speech processors on the optimum sensitivity setting and with the Institute of Hearing Research (IHR)/McCormick Automated Toy Discrimination Test¹ warble tone facility. The warble generator provides sound field warble tones at 7 frequencies from 0.25 to 5 kHz at levels from 0 to 78 dB (A) in steps down to 1 dB. The frequency modulation depth was 10%, and the modulation rate was 10 Hz. Calibration was achieved by positioning a microphone in the same position that the child's head was located for testing. The loudspeaker was placed so that its central axis was aligned with the microphone, 1 m away. All tests were undertaken in identical sound-attenuated booths/clinics, with an ambient noise level of 17 dB (A). Positioning of the loudspeakers and calibration microphone was identical in each testing room. Speech discrimination performance was obtained by use of the IHR/McCormick Automated Toy Discrimination Test. The recorded single-word stimuli were presented by means of a loudspeaker, and the response was encoded by the tester's handset. An adaptive procedure² was used to calculate the level in dB (A) at which the subject obtained a 71% speech discrimination score (that is, correctly identified the words with an accuracy of 71% for 6 reversals using an adaptive threshold chasing technique).

Procedure. All children were initially fitted with the SPrint processor and then converted to the ESPrIt. All children were programmed in monopolar + 1 stimulation mode. The map parameters were the same, as was the sensitivity setting. Conversion was not attempted until the maps were considered optimal. During the early stages of mapping with young children, the comfort levels were investigated very cautiously. In general, these levels changed and were increased over time as the child adjusted to, and accepted, more stimulation. The map was considered optimized when both threshold and comfort levels had stabilized and were measured at consistent levels over several months. Conversion was attempted on 4 children after 12 weeks' experience with the SPrint processor, and conversion was attempted on 2 more children after 26 and 52 weeks' experience with the SPrint processor, respectively. At the time of conversion, aided sound field thresholds and speech discrimination scores were collected with both devices. The order of task presentation was counterbalanced across children to minimize fatigue effects.

RESULTS

Fitting Success. Five of the 6 children were fitted successfully and are using the device consistently. One child could not be fitted with the ESPrIt because of difficulties

with the channels' being out of compliance. With her initial SPrint map, 4 channels were out of compliance, and they were deactivated 12 weeks after initial stimulation with the monopolar + 1 stimulation mode and a pulse width of 25 μ s. Twelve months after the fitting, conversion to the ESPrIt was attempted for the 18 active channels with the WinDPS system on the basis of Monopolar + 1 data, but fitting was not possible because of high voltage compliance on the majority of channels. Subsequently, the child's implant was remapped with the monopolar 1 + 2 stimulation mode, but conversion was still not possible because of high voltage compliance on the majority of channels (more than 12 channels with a pulse width of 25 μ s and an interstimulus pulse gap of 45 μ s). A minimum of 12 channels within compliance is required to fit the ESPrIt. Eighteen months after the fitting, conversion was attempted with a wider pulse width, but problems were still encountered for this child, preventing the use of this case for the present study. Further investigations will be made to achieve conversion for a subsequent study.

Difficulties Encountered. Difficulties were categorized as processor or software problems. The processor problems included intermittent "noise" perceived by 1 patient, "cutting out" alleviated by switching the processor off and back on again, variable battery life, and moisture ingress. Software programming difficulties were encountered because it was initially unclear from the manufacturer's guidelines whether to set the base level at 4 or at 10 for ESPrIt processors and whether to program in monopolar + 1 or monopolar 1 + 2 stimulation mode. Subsequent advice from the manufacturer indicated that the base level should be set to 4, with the monopolar 1 + 2 stimulation mode as the recommended option.

Aided Thresholds and Speech Discrimination Performance. The early results show that the ESPrIt device performs as well as the SPrint, and there is an indication of improved performance for the ESPrIt at 4 kHz (paired *t*-tests, $p < .05$). For the other frequencies, and for speech discrimination, there is a nonsignificant trend toward improved thresholds for the ESPrIt relative to the SPrint (Table 2).

DISCUSSION

The preliminary results on aided sound field warble tone thresholds and speech discrimination scores indicate that the ESPrIt is performing as least as well as the SPrint. Indeed, there are early indications that the ESPrIt is providing more gain, with a significant difference found at 4 kHz. Further follow-up and larger numbers of children in the ongoing study may confirm these possible gains.

Advantages of ESPrIt Processor. The 5 children fitted with the ESPrIt prefer it to the SPrint. It has cosmetic benefits, and the children have greater freedom to participate in sports. Parents and children made the following comments: "Wears it as he goes to sleep," "More freedom playing sports, no box banging around," "Wears it all the time, very pleased with it," and "The ESPrIt is louder and clearer compared with the SPrint."

Limitations of ESPrIt Processor. The ESPrIt does not currently support an FM device. This is an important limi-

tation, in that one quarter of the children in the Nottingham program have been fitted with an FM system in conjunction with their body-worn speech processors. It is expected that the number of FM users will increase as the children's educational setting changes with age. Therefore, because of the ESPrit's lack of FM input, 2 processors (ESPririt and SPrint) are currently required for any child who uses the ESPrit and an FM radio hearing aid, and this adds to the cost borne by implant programs. An acoustic cochlear implant-FM coupler could be developed and used as an interim measure before the system becomes fully compatible with normal FM input. A further limitation of the ESPrit is that there is no visible check of processor function for inexperienced users.

Recommendations for Improvement. To aid audiologists in tuning the device, clear manufacturer's guidelines for fitting the ESPrit are needed, with details of the map parameter values that may ensure ESPrit fitting. In addition, retainers should be provided to secure the ear-level device, a sensitivity control lock is needed to avoid inadvertent manipulation by the children (we believe a solution to this is pending), and a battery compartment lock is required for young children. Furthermore, visible battery

warning signals for cutout should be available. Such visible checks of device function are required for parents and teachers of young and inexperienced users.

Cautions for Fitting Very Young Children or Inexperienced Listeners. Initial fitting with the ESPrit is not recommended. This is based on experience with 1 child who has, so far, been unable to convert to the ESPrit device. This child needed some 12 weeks' experience with the SPrint before an optimum map could be established. Initial fitting of this child with an ESPrit would have probably resulted in a nonoptimal map's being provided, which might have limited subsequent performance. Another reason initial fitting with the ESPrit is not recommended is that there is no visible check to monitor device function and no ability to listen to the microphone.

ACKNOWLEDGMENTS — We acknowledge the considerable support of Dr Ken Robinson to this study, and we are grateful to Cochlear UK (Ltd) for device support to aid this project.

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SPEECH PERCEPTION RESULTS IN CHILDREN USING THE CLARION® MULTI-STRATEGY™ COCHLEAR IMPLANT

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INTRODUCTION

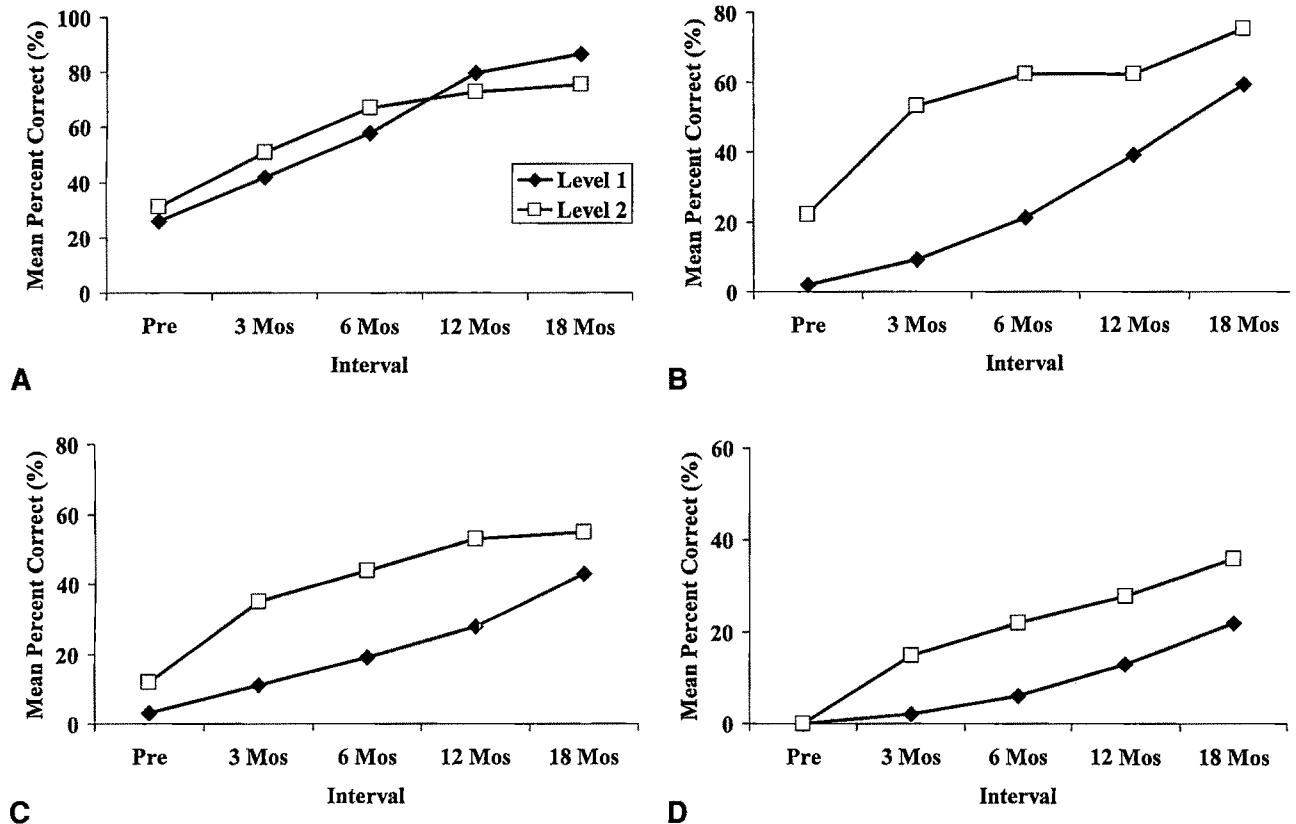
Research and clinical experience have established that profoundly hearing-impaired children derive substantial benefit from multichannel cochlear implants. Because most children who are implant candidates become deaf before speech and language are developed, it is crucial to determine whether the information transmitted by a multichannel cochlear implant is sufficient for them to learn the auditory code underlying spoken language. Previous research has shown that acquisition of auditory and language skills develops over many years in children who receive multichannel cochlear implants.¹⁻⁵ The children in most previous studies, however, used older implant technology and speech processing schemes that encoded relatively limited acoustic speech information (ie, speech features). Although the results of these studies showed a wide range of postimplant performance, the general trends were that closed-set word identification skills did not emerge until after at least 1 year of implant use and open-set skills developed over an even longer time course. Unlike the previous generation of implant processing schemes, current implant strategies encode the entire speech waveform to provide the listener with as much detail as possible about the incoming acoustic signal. Relatively little is known about the auditory perceptual benefits derived by children implanted with these newer speech processing schemes. Such information is of fundamental impor-

tance to the field, especially if faster learning rates and overall higher levels of performance are achieved with improved signal processing in implants.

The purpose of the present study is to examine the performance of children implanted with the CLARION® Multi-Strategy™ Cochlear Implant during the clinical trial of the device in the United States. Since the time of the commercial approval of the device by the US Food and Drug Administration, a postmarket surveillance study has been conducted to monitor the long-term effectiveness of the Clarion in the first group of children fitted with implants during the clinical trial. This report summarizes the speech perception performance of 58 prelingually deafened children who have used their Clarion implants for 18 months. All children used the Continuous Interleaved Sampler (CIS) strategy in their implants. It is a high-rate, nonsimultaneous pulsatile strategy.⁶

METHODS

The study group consisted of 58 children, consecutively implanted with the Clarion 1.2 device during the clinical trial in the United States, who had used their implant for 18 months at the time of this report. A repeated-measures design was used to compare the children's preoperative performance with hearing aids with their postoperative performance with the Clarion after 3, 6, 12, and 18 months of use. The same study sample was evaluated at each in-



Group mean scores (percent) for children evaluated on Level 1 ($n = 36$) or Level 2 measures ($n = 22$). A) Monosyllable Word Identification subtest of Early Speech Perception test. B) GASP word test. C) PBK phoneme test. D) PBK word test.

interval, although there are instances of missing data for some children resulting from missed appointments or other unavoidable circumstances.

Closed- and open-set speech recognition tests typically used to evaluate implant benefit were used in the study. Level 1 tests were administered to all children younger than age 4. Level 2 tests were administered to all children 7 years of age and older. Children ages 4, 5, and 6 were administered a screening test to determine the appropriate test level. Closed-set word identification was assessed with the Monosyllable Word Identification subtest of the Early Speech Perception (ESP) test.⁷ The Low Verbal Version, consisting of 4 objects (3 repetitions of each of 4 items; chance = 25%), was used for Level 1 testing. The Standard version, consisting of 12 pictured words (2 repetitions of each word; chance = 8%), was employed for Level 2 testing. The Glendonald Auditory Screening Procedure (GASP) word test is an open-set test consisting of 12 words of different syllable number or stress pattern (chance = 0%).⁸ The Phonetically Balanced-Kindergarten (PBK) test consists of lists of phonetically balanced monosyllabic words taken from the vocabulary of normal-hearing 5-year-old children.⁹ Half-lists of 25 words were presented and scored for the number of phonemes and words correctly identified (chance = 0%). No modifications were made on the GASP word or PBK test for Level 1 testing. All tests were administered by means of listening alone with live-voice presentation.

Thirty-six children were administered Level 1 measures

(mean age at implantation, 3.4 years; mean age at onset of deafness, 3 months; mean preoperative unaided pure tone average in the implant ear, 111 dB hearing level [HL]). Twenty-two children were administered the Level 2 tests (mean age at implantation, 8.6 years; mean age at onset of deafness, 1.6 years; mean preoperative unaided pure tone average in the implant ear, 108 dB HL).

RESULTS AND DISCUSSION

The results revealed a significant improvement in mean scores over time on all measures for both groups of children ($p < .001$), indicating that they obtained more benefit from their cochlear implants than from conventional hearing aids. The mean scores on the measures, shown in the Figure, suggest evidence of closed- and open-set speech recognition skills after relatively limited implant experience (ie, 3 to 6 months of use).

The Figure, A, shows the mean scores for the 2 groups of children on the ESP Monosyllable Word Identification test. On this measure, there was no significant difference in the mean scores of the 2 groups of children, presumably because the subtests (ie, Low Verbal and Standard versions) were developmentally appropriate for each group. The Figure, B-D, summarizes performance on the open-set tests on which the mean scores of the children tested on the Level 2 measures were significantly higher than those of the children tested on the Level 1 tests. These group differences presumably reflect developmental issues involving the vocabulary and response tasks of the

DESCRIPTIVE STATISTICS FOR CHILDREN AFTER 18 MONTHS OF CLARION USE

Test	Mean	SD	Percentiles		
			25th	50th	75th
Implantation at mean age of 3.4 y					
Monosyllable Word test	87	24	83	100	100
GASP word	59	37	13	75	92
PBK phoneme	28	29	0	17	49
PBK word	22	22	0	22	32
Implantation at mean age of 8.6 y					
Monosyllable Word test	76	27	53	85	100
GASP word	75	30	50	92	100
PBK phoneme	55	33	29	67	84
PBK word	36	31	2	40	60

tests, rather than differences in degree of implant benefit derived by the younger and older children.

The Table shows the descriptive statistics at the 18-month interval for the children administered the Level 1 and Level 2 tests. These data illustrate the range in performance demonstrated by the children, a finding consistent with the results of previous investigations.¹⁻⁴ Examination of the variables contributing to individual differences in performance is addressed in the study reported by Osberger and Fisher (this supplement, pp 44-46).

In summary, the results suggest faster rates of learning in children who use current implant technology than was demonstrated with previous speech processing schemes. After 18 months of implant use, however, the performance of the children fitted with implants at an older age remains higher than that of the children fitted with implants at a younger age. The difference between the older (Level 2) and younger (Level 1) children appears to be decreas-

ing over time, suggesting that the performance of the children fitted with implants at a younger age may ultimately exceed that of the children fitted with implants at an older age. Previous studies have shown, however, that 2 or more years of implant use may be required before an effect of age at implantation is observed on open-set measures.⁵

ACKNOWLEDGMENTS — We thank the surgeons and audiologists at the 25 investigational centers in the clinical trial for their efforts in patient enrollment, patient management, and data collection.

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SPEECH PERCEPTION IN YOUNG CHILDREN USING NUCLEUS OR CLARION COCHLEAR IMPLANTS: EFFECT OF COMMUNICATION MODE

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INTRODUCTION

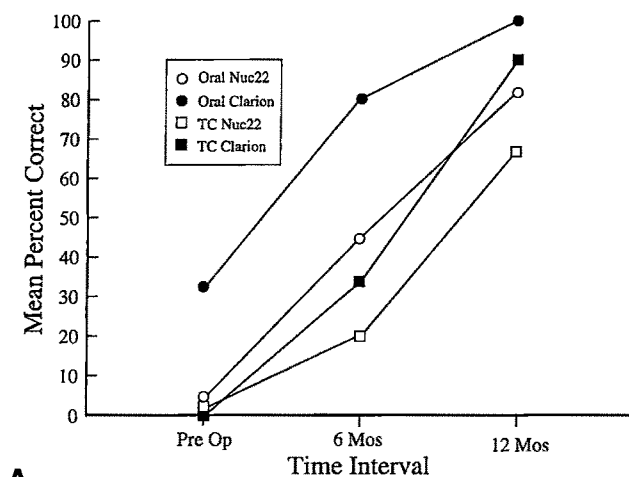
In a previous report, we compared the speech perception skills of 43 congenitally deaf children who were implanted before age 5 with the Nucleus 22 (spectral peak [SPEAK] strategy) cochlear implant, or the CLARION® Multi-Strategy™ Cochlear Implant (Continuous Interleaved Sampler [CIS] strategy).¹ The results revealed higher mean scores on all tests for the Clarion users than for the Nucleus users during the first year of implant use. The present study extends these analyses to examine the effect of communication mode, as well as device type, on the development of auditory perceptual skills in these 43 children during the first year of implant use.

METHODS

The subjects consisted of 43 children fitted with implants at Children's Memorial Medical Center in Chicago,

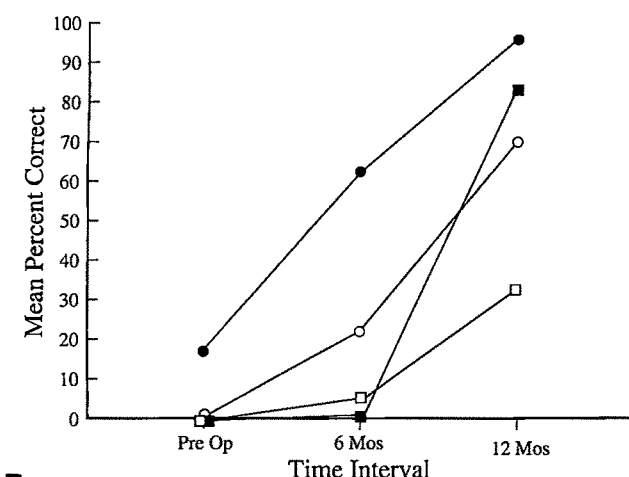
Ill, or at the University of North Carolina who met the following inclusion criteria: 1) under 5 years of age at time of implantation, 2) congenitally deaf, 3) radiographically normal cochleas, 4) English as the primary language of the family, 5) absence of medical conditions likely to impede progress, 6) speech coding strategy experience limited to SPEAK for the Nucleus 22 or CIS for the Clarion.

Twenty-three children were implanted with the Nucleus 22, and 20 with the Clarion device. There was no significant difference in mean age at implantation by device or by communication mode (Nucleus means, 3.0 and 3.1 years for communication and total communication [TC], respectively; Clarion means, 3.1 and 3.5 years). Children in the oral education group included those using auditory-oral, auditory-verbal, or cued speech communication methods during the first 12 months after implantation. Oral

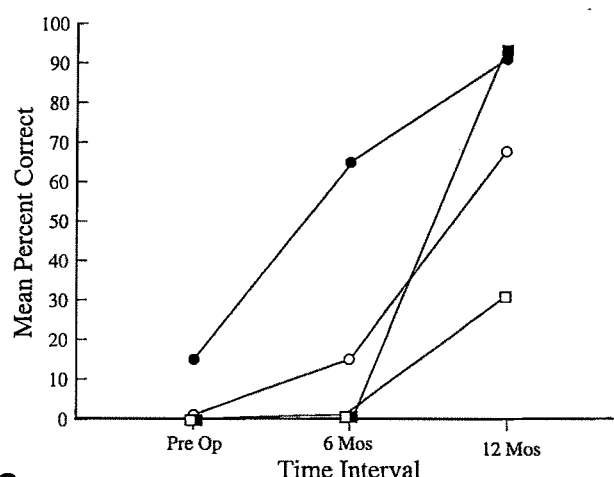


A

Mean scores on Central Institute for the Deaf Early Speech Perception battery by device and communication mode. A) Pattern perception. B) Spondee. C) Monosyllable.



B



C

children included 11 Nucleus 22 and 12 Clarion recipients. Twelve Nucleus 22 subjects and 8 Clarion subjects used TC.

Descriptive and inferential statistical analyses were performed with 2-way analysis of variance and independent group *t*-tests to compare groups. The criterion for statistical significance was set at $p \leq .05$, two-tailed.

Before implantation, the oral children demonstrated statistically significantly better aided thresholds at 500 Hz (mean, 57.4 dB) and 1,000 Hz (mean, 63.4 dB) and a better pure tone average (mean, 68.7 dB) than did children who used TC (means, 73.5, 73.3, and 76.3 dB, respectively). There were no differences in the preoperative thresholds of the Nucleus 22 users by communication mode. However, oral children who received the Clarion had significantly better preoperative aided thresholds at 250 Hz, 500 Hz, and 1,000 Hz (means, 48.8, 52.5, and 55.5 dB, respectively) than did Clarion children who used TC (means, 61.9, 75.6, and 74.4 dB, respectively).

Oral children who received the Clarion had significantly better unaided thresholds at 250 Hz (mean, 85.8 dB) and better aided thresholds at 1,000 Hz (mean, 55.5 dB) than oral children who received the Nucleus 22 device (means, 101.5 and 71.4 dB, respectively). There was no difference in hearing levels of TC children who used the Nucleus

22 device versus the Clarion device.

Performance on the 3 subtests of the Central Institute for the Deaf Early Speech Perception (ESP)² battery (pattern perception, spondee word identification, and monosyllable word identification) was examined after 6 and 12 months of implant use. There were no significant differences in the preoperative scores on the 3 ESP subtests as a function of device or communication mode.

RESULTS

Speech perception test scores over time as a function of device and communication mode are shown in the Figure for pattern perception, spoken word identification, and monosyllable word identification. There were significant differences between the mean scores of oral and TC children, combined across device, on the pattern perception ($p < .05$), spondee ($p < .000$), and monosyllable ($p < .001$) subtests after 6 months of implant use. At the 12-month interval, the only significant difference by communication mode was on the spondee test ($p < .05$).

Analysis of variance also showed a significant interaction of communication mode and device on spondee and monosyllable scores at 6 months. There were no significant differences between the scores of the oral and TC children at either interval for the Nucleus 22 group. For

the Clarion children, the mean scores of the oral children at 6 months were significantly higher than those of the TC children on all 3 subtests. By the 12-month interval, differences were no longer present, and the mean scores of both groups were close to the ceiling of each measure.

DISCUSSION

The perception skills of the TC children were very limited after 6 months of implant use, with essentially no closed-set word identification skills. In contrast, the oral children showed modest word identification skills after a comparable duration of implant use. By the 12-month interval, the TC children had made substantial gains in auditory skills and appeared to be "catching up" to the oral children, although this was most marked within the Clarion group. The mean scores of the oral children suggest that many of them have reached the ceiling of the 3 tests after 12 months of device use.

These results suggest that children who use oral communication acquire auditory perception skills with their implants at a faster rate than do children who use TC, a finding that has been reported by other investigators.³⁻⁵ We assume this is a result of differences in the amount of auditory training received in the 2 types of education programs. However, no quantitative data are available regarding amount of auditory training, nor do we have data regarding other possible confounding factors, such as intellectual status.

Analysis of our data showed a significant interaction between communication mode and device type on the spondee and monosyllable word identification subtests at the 6-month interval. These results suggest that oral children who use the Clarion-implant demonstrate faster learning rates than do TC children who use the Clarion. Oral children who use the Nucleus 22 implant, however, did not demonstrate this same advantage over their peers who use TC.

There were a few differences in preoperative aided thresholds between oral and TC children and between oral children using the Nucleus 22 device and those using the Clarion, with oral children and Clarion children having

better thresholds. Therefore it is possible that residual hearing, or the nerve survival it represents, plays a role in speech perception with a cochlear implant. However, the threshold differences did not result in any significant differences in preoperative speech perception abilities, or even in preoperative aided speech awareness threshold. In a previous study that included many of the same children, a multiple regression analysis was used to examine factors predictive of implant performance. For performance at 6 months, preoperative aided speech awareness threshold and ESP test performance both contributed somewhat to predicting implant performance.⁵ Neither of these factors differed between groups in the present study. As children with more residual hearing receive implants, this may be an important predictor of performance. However, because those with better hearing are more likely to choose oral education programs, it may remain difficult to tease out the relative importance of these 2 factors.

The findings in the current study are consistent with those of the past, indicating faster learning rates for some oral children in the short term (6 months) than for TC children. But it is also exciting to note the improvement that TC children can make by 12 months.

ACKNOWLEDGMENT — We thank Karen Berliner, PhD, for her advice and assistance in the statistical analysis of the data.

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SPEECH PERCEPTION IN CHILDREN WITH COCHLEAR IMPLANTS: EFFECTS OF LEXICAL DIFFICULTY, TALKER VARIABILITY, AND WORD LENGTH

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INTRODUCTION

Spoken word recognition by cochlear implant recipients traditionally has been assessed with the Phonetically Balanced-Kindergarten (PBK) word lists.¹ However, many children with cochlear implants perform relatively poorly on the PBK.²⁻⁵ One difficulty with the PBK is that the

test items may be unfamiliar to children with profound hearing loss, who often have limited vocabularies. Furthermore, although the PBK provides descriptive information about children's speech perception abilities, it yields little insight into factors that influence their spoken word recognition.

TABLE 1. PARTICIPANT CHARACTERISTICS

	Oral (N = 14)	Total Communication (N = 14)
Age at onset (y)	0.1 ± 0.2	0.6 ± 0.9
Age at implantation (y)	5.0 ± 1.8	4.3 ± 1.6
Age at testing (y)	8.2 ± 1.8	8.8 ± 1.9
Length of implant use (y)	3.3 ± 1.5	4.5 ± 1.5
Unaided PTA (dB HL)	108 ± 5.7	114 ± 5.0
Data are mean ± SD.		
PTA — pure tone average, HL — hearing level.		

In listeners with normal hearing, both the lexical characteristics of the stimuli (word frequency and lexical density) and the presence of talker variability influence spoken word recognition.⁶⁻¹¹ Findings from listeners with normal hearing indicated that lexically easy words (ie, those that occur more often and have few phonetically similar words, or neighbors, with which they can be confused) are identified with greater accuracy than lexically hard words (those that occur less often and have many lexical neighbors).^{8,9} In addition, as the number of talkers increases, generally, word identification decreases and response latency increases.^{10,11} At Indiana University, we have developed new lexically controlled, recorded word lists incorporating stimulus variability to evaluate open-set speech recognition by listeners with cochlear implants or other sensory aids. In the present study, these recorded word lists were used to assess the effects of lexical difficulty, talker variability, and word length on spoken word recognition by pediatric cochlear implant recipients.

METHODS

Participants. All participants were selected from the group of children with implants enrolled in the longitudinal study of speech perception under way at Indiana University School of Medicine. All participants were prelingually deafened (<3.0 years) and were at least 5 years of age at the time of testing (N = 28). Demographic data are summarized in Table 1. All but 1 child used the Nucleus 22-channel cochlear implant system, 23 with the spectral peak processing strategy, and 4 with the multiplex strategy. The remaining child used the Clarion cochlear implant system with the Continuous Interleaved Sampler strategy.

Stimulus Materials. The Lexical Neighborhood Test (LNT) and the Multisyllabic Lexical Neighborhood Test (MLNT)¹² were used to assess spoken word recognition. The test items were drawn from words produced by children between the ages of 3 and 5 years¹³ and were assumed to represent early-acquired vocabulary. The LNT consists of two 50-item monosyllabic word lists, and the MLNT contains two 24-item multisyllabic word lists. In each of the 4 lists, half of the items are lexically easy and half are lexically hard.

The 100 LNT and the 48 MLNT stimulus words were recorded by 3 male and 3 female talkers using a conversational speaking style. The productions were digitized at a 20-kHz sampling rate and edited to remove silence preceding or following each token. The edited speech

TABLE 2. PERCENTAGE OF WORDS CORRECTLY IDENTIFIED ON LNT AND MLNT IN TWO TALKER CONDITIONS

Test	Single-Talker	Multiple-Talker
LNT		
Easy words	35.0 ± 4.9	42.3 ± 4.9
Hard words	25.1 ± 4.0	30.0 ± 4.0
MLNT		
Easy words	46.5 ± 4.9	49.8 ± 4.9
Hard words	30.9 ± 4.0	38.3 ± 4.0

Data are mean ± SD in percent.

LNT — Lexical Neighborhood Test, MLNT — Multisyllabic Lexical Neighborhood Test.

waveforms were then stored as individual digital files for later computer presentation.

The intelligibility of each talker was evaluated in a pilot study conducted with 60 normal-hearing adults listening in quiet; a different group of 10 listeners was used for each of the 6 talkers. All talkers were highly intelligible to the listeners with normal hearing; the mean intelligibility score across the 6 talkers was approximately 97% words correct. On the basis of these results, single-talker and multiple-talker versions of each LNT and MLNT word list were created. Tokens from 1 male talker were used for the single-talker conditions, because his individual intelligibility score in the pilot study was closest to the mean for the 6 talkers. The remaining 5 talkers contributed tokens to the multiple-talker conditions.

Procedures. The testing was conducted in a quiet room by an examiner who sat to one side of the child. The stimuli were presented at 70 dB sound pressure level by means of a loudspeaker placed at 0° azimuth from the child. Each participant was administered 1 LNT and 1 MLNT word list in a single-talker condition, and the remaining LNT and MLNT lists in the multiple-talker condition. Test order, list number, and talker condition were counterbalanced across children. The participants responded by repeating the word they heard. The responses were scored as the percentage of lexically easy and hard words correctly identified in each talker condition. Four paired *t*-tests were used to evaluate separately the effects of lexical difficulty within each talker condition (LNT-st, LNT-mt, MLNT-st, MLNT-mt). The data were subjected to a 2-way repeated-measures analyses of variance (RM-ANOVA) with talker condition (single versus multiple) and word length (monosyllabic versus multisyllabic) as the independent variables. Separate RMANOVAs were computed for the lexically easy and hard words.

RESULTS

Table 2 presents the mean percentages of words correctly identified on the LNT and MLNT as a function of lexical difficulty and talker condition. The results demonstrate that lexically easy words are recognized with significantly greater accuracy than lexically hard words (*p* < .002). Further, the effects of lexical difficulty were significant regardless of talker condition or length of the stimulus words. For both the LNT and MLNT, word recognition was significantly higher in the multiple-talker condi-

tion than in the single-talker condition ($p < .04$). The results also demonstrated that multisyllabic words were identified with significantly greater accuracy than monosyllabic stimuli ($p < .002$). The effects of word length do not depend on the number of talkers presenting the stimuli.

SUMMARY AND CONCLUSIONS

The present results demonstrated that all 3 factors — lexical difficulty, stimulus variability, and word length — significantly influenced spoken word recognition by children with multichannel cochlear implants. Lexically easy words were recognized significantly better than lexically hard words, regardless of talker condition or word length of the stimuli. These results support the earlier findings of Kirk et al¹² obtained with live-voice stimulus presentation and suggest that lexical effects are very robust. Despite the fact that listeners with cochlear implants receive a degraded speech signal, it appears that they organize and access words from memory relationally in the context of other words.

The present results concerning talker variability contradict those previously reported in the literature for listeners with normal hearing^{7,11} and for listeners with mild-to-moderate hearing loss who use hearing aids.¹⁴ The previous investigators used talkers and word lists different from those used in the current study and found that word recognition declined as talker variability increased. In the current study, word recognition was better in the multiple-talker condition than in the single-talker condition. Kirk¹⁵ reported similar results for postlingually deafened adults with cochlear implants who were tested on the recorded word lists used in the present study. Although the talkers were equally intelligible to listeners with normal hearing in the pilot study, they were not equally intelligible to children or adults with cochlear implants. It appears that either the man in the single-talker condition was particularly difficult to understand or that some of the talkers in the multiple-talker condition were particularly easy to understand. Despite the unexpected direction of the talker effects, the present results demonstrate that children with cochlear implants are sensitive to differences among talkers and that talker characteristics influence their spoken word recognition. We are conducting a study to assess the intelligibility of each of the 6 talkers to listeners with cochlear implants. Such studies should aid the development of equivalent testing conditions for listeners with cochlear implants.

There are 2 possible reasons the children in the present study identified multisyllabic words better than monosyllabic words. First, they may use the linguistic redundancy cues in multisyllabic words to aid in spoken word recognition. Second, multisyllabic words come from relatively sparse lexical neighborhoods compared with monosyllabic tokens. That is, multisyllabic words have fewer phonetically similar words, or neighbors, competing for selection than do monosyllabic stimuli. These lexical characteristics most likely contribute to the differences in identification noted as a function of word length.

The significant lexical and word length effects noted

here may yield important diagnostic information about spoken word recognition by children with sensory aids. For example, children who can make relatively fine phonetic distinctions should demonstrate only small differences in the recognition of lexically easy versus hard words or of monosyllabic versus multisyllabic stimuli. In contrast, children who process speech using broad phonetic categories should show much larger differences. That is, they may not be able to accurately encode words in general or lexically hard words specifically. Further study is warranted to determine the interaction between spoken word recognition and individual word encoding strategies.

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SPEECH PERCEPTION BY PRELINGUALLY DEAF CHILDREN AFTER SIX YEARS OF COCHLEAR IMPLANT USE: EFFECTS OF AGE AT IMPLANTATION

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INTRODUCTION

It is clear that even children with prelingual deafness can obtain significant benefits from cochlear implants.¹⁻⁷ In this report, we provide some additional long-term data on children who have used their implants for over 6 years.

METHODS

Of 95 children who received Cochlear Corporation cochlear implants at the University of Iowa (83 with the Nucleus 22, and 21 with the Nucleus 24), in this paper we focus on 26 prelingually deaf children who have used their Nucleus 22 device for 6 years (see Fryauf-Bertschy et al² for additional details). Twenty-four are enrolled in total communication programs, and 2 are now in oral programs.

The children were tested in a sound-treated room and were tested with either live voice or with computer-based recorded stimuli. The stimuli were presented at about 70 dB sound pressure level. The details of the tests used and the testing protocols were given by Fryauf-Bertschy et al² and Tyler.⁸

RESULTS

Average Performance at Six Years. Figure 1 displays the average results for several of our speech perception tests after 6 years of implant use. The easiest test is the Monosyllable-Trochee-Spondee stress test,⁹ with average scores of 91% correct. Many children have scored 100%

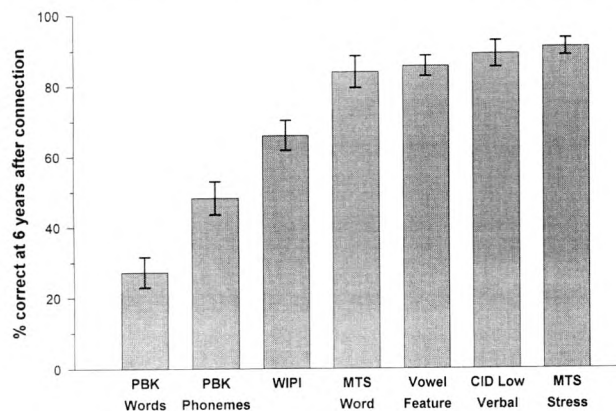


Fig 1. Average results after 6 years of implant use. Height of each line at top of bars represents 1 standard deviation on this and subsequent Figures. Same 26 subjects underwent each test. PBK — Phonetically Balanced–Kindergarten, WIPI — Word Intelligibility by Picture Identification, MTS — Monosyllable-Trochee-Spondee, CID — Central Institute for the Deaf.

correct on this test, and these average scores are therefore influenced by ceiling effects. The most difficult test is the Phonetically Balanced–Kindergarten (PBK) open-set word recognition test,¹⁰ with scores averaging 27%. Of these 26 children, 20 scored 10% or above on this open-set word recognition test.

Average Performance as Function of Time. Figure 2^{8,10} displays the average results over time. For each test, the same children were tested at each test interval. As expected, a stress test is the easiest, open-set word recognition is the most difficult, and closed-set speech tests fall between the two. In the first 12 months of implant use, increases are apparent on all tests except word recognition. In the first 3 years of implant use, it is possible to observe increases in performance. Beyond 3 years, ceiling effects restrict our ability to observe changes on the easier tests. On the most difficult test, increases in average performance are observed out to 5 years.

Effects of Age at Implantation. So far, we have been examining group data in which we have ignored the age at implantation. Now, we divide the data into 4 groups according to the age at which the subjects received their cochlear implants, and individual performance is plotted over time (see also Fryauf-Bertschy et al²). There are only small numbers of children in each group, so these observations must be considered preliminary. Results are shown from the word recognition PBK test (Fig 3).

For the first 2 years of implant use, it is difficult to

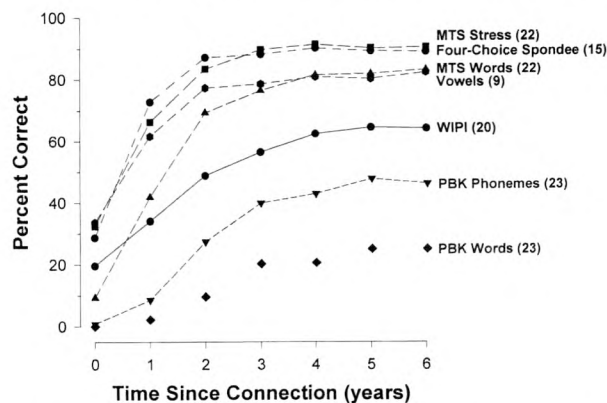


Fig 2. Average results from variety of tests over 6-year period. Tests include MTS tests scored by stress and by word, 4-choice spondee test, Iowa Vowel Test,⁸ WIPI, and PBK¹⁰ scored for phonemes and words. Within each test, same group of subjects had data points for all time intervals. Number of children tested is in parentheses.

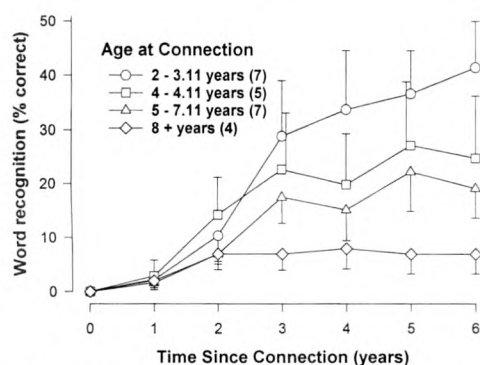


Fig 3. Average results of PBK word recognition test over time. Children are grouped by age at implantation.

determine whether differences exist among the groups. By the third year, however, children fitted with implants at a younger age obtained higher scores than those fitted with implants at an older age. Although the number of children in each group is small, the order is observed from 3 to 5 years. Note also that the children fitted with implants before the age of 4 years show continued increases in performance at least up to 6 years.

Consonant Audiovisual Feature Perception. Figure 4 shows the average results from the 10-choice Audiovisual Feature Test⁸ for 18 prelingually deaf children who had used their implants for 6 years. Audition-alone and vision-alone scores are about 40% correct on average. Note the small variability on the vision scores, indicating that lipreading performance across children is similar. Audition-plus-vision scores are about 77% correct, indicating a high degree of audiovisual enhancement provided by the implant.

DISCUSSION

Factors Involved in Speech Perception. Several factors contribute to the performance of children with cochlear implants.

1. Differences in fitting expertise.
2. Differences in educational settings. (Our children are mostly from total communication situations.)
3. Differences in selection criteria. (Selection criteria were more conservative 6 years ago than they are today.)
4. Differences in processors. (Recent results suggest that average results with the spectral peak processor are better than those obtained with previous processors.)
5. Differences in test protocols. (Results are lower with unfamiliar talkers; there may be differences in judgments about correct responses by testers.)
6. Differences in subject pools. (Families from higher socioeconomic backgrounds may be expected to score higher.)
7. The amount of rehabilitation received.

The levels of speech perception ability observed here provide the important basis for changes observed in these same children in speech production,¹¹ language,¹² psychological (Knutson et al, this supplement, pp 100-103), and

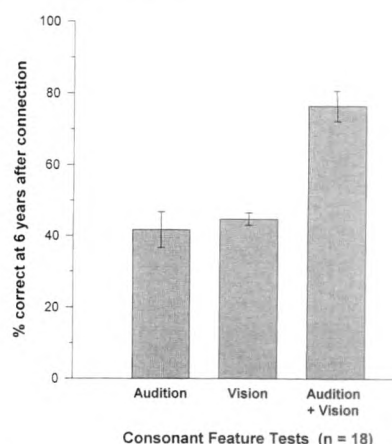


Fig 4. Average results of Iowa Audiovisual Consonant Test for 18 implanted children with 6 years of cochlear implant use.

educational¹³ abilities.

Summary of Key Observations. These results indicate the following.

1. There is a wide range of performance across different children.
2. Some children require several years of implant use to show improvements in open-set word recognition.
3. Small but consistent gains are observed in average results 4, 5, and 6 years after implantation. In addition, there may be other aspects of speech perception, not measured by these tests, that are continually being enhanced throughout this period.
4. Children fitted with implants at a younger age show more rapid learning curves than children fitted with implants at an older age. However, it also must be emphasized that children who receive their implants at a later age also show important, significant benefit from their implants.
5. Prelingually deaf children educated with total communication show audiovisual enhancement after cochlear implantation. This is particularly noteworthy, because the information on the lips is not synchronized with the hand movements. It may be that larger gains in audiovisual enhancement, or at least enhancement at shorter postimplant intervals, will be observed in implanted children who are trained in an oral setting.

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INTERPOLATION WITH THE NUCLEUS 22 COCHLEAR IMPLANT

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INTRODUCTION

With young children, it may take many sessions to tune their cochlear implants. The software for the CLARION® Multi-Strategy™ Cochlear Implant offers interpolation—after threshold and comfort levels are established for any 2 channels, the software estimates the settings for the intermediate channels. A similar option would be appealing for the Nucleus implant, with its many channels, if interpolation were sufficiently precise. But there can be considerable variation in threshold (T) and maximum comfort (C) levels from one electrode to the next for many reasons. Survival of dendrites and cell bodies varies from place to place within the cochlea.¹ The insulating properties of the bony labyrinth are believed to affect threshold in a complex manner: the bone confines the current within the membranous labyrinth, reducing spread away from the neurons, but it may also insulate the spiral ganglion from the electrodes. The proximity of the electrodes to the neurons varies along the length of the array.² Finally, stimulus mode affects variability. In bipolar mode, the current density drops off much more rapidly with distance than in monopolar mode, so small variations in electrode-to-nerve distance are more critical.³

To determine whether interpolation has promise, the procedure was modeled from the maps of children fitted with the Nucleus 22 cochlear implant. Two issues were addressed. First, with linear interpolation, what biases or systematic errors result? Second, if interpolated maps are adjusted to account for these biases—if the interpolated maps were corrected to take into account the shape of the typical map—how much do the estimated values still vary from the actual maps?

PATIENTS AND METHODS

Subjects. The maps of 20 children were examined. All had insertions of at least the 22 active electrodes, and all were programmed in bipolar + 1 (BP + 1) mode. Maps were selected from the next tuning session after the first year of use. This interval, rather than a shorter one, was used to minimize variation due to unfamiliarity with stimulation; this inquiry is concerned with the best-case precision of interpolation, separate from other sources of imprecision.

Linear Interpolation. The results of linear interpolation were compared with actual T and C levels, as functions of the number of interpolated electrodes; for ex-

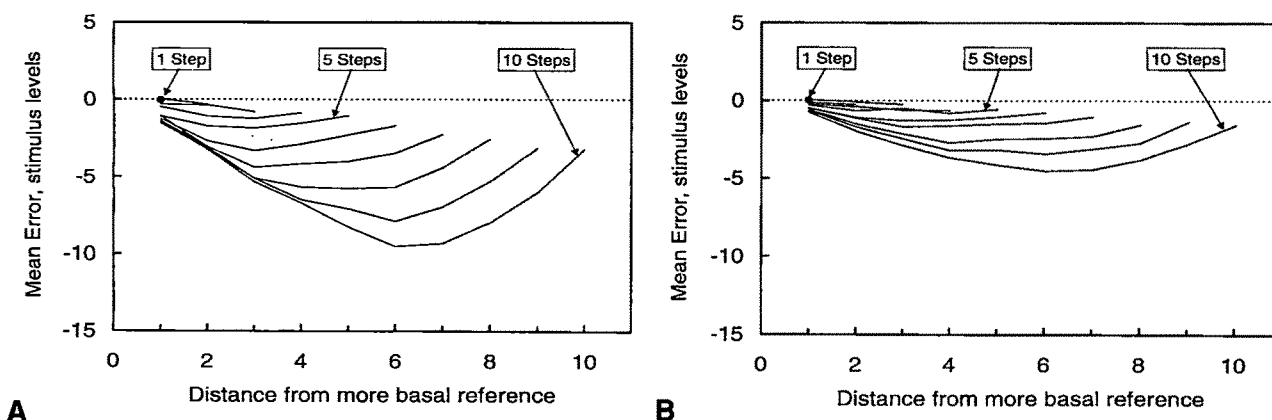


Fig 1. Mean discrepancies between estimated and actual A) maximum comfort (C) levels and B) threshold (T) levels are shown for linear interpolation across various numbers of electrodes. Linear interpolation tended to underestimate levels because of shape of typical map. This bias can be eliminated by adjusting interpolated values according to normative map.

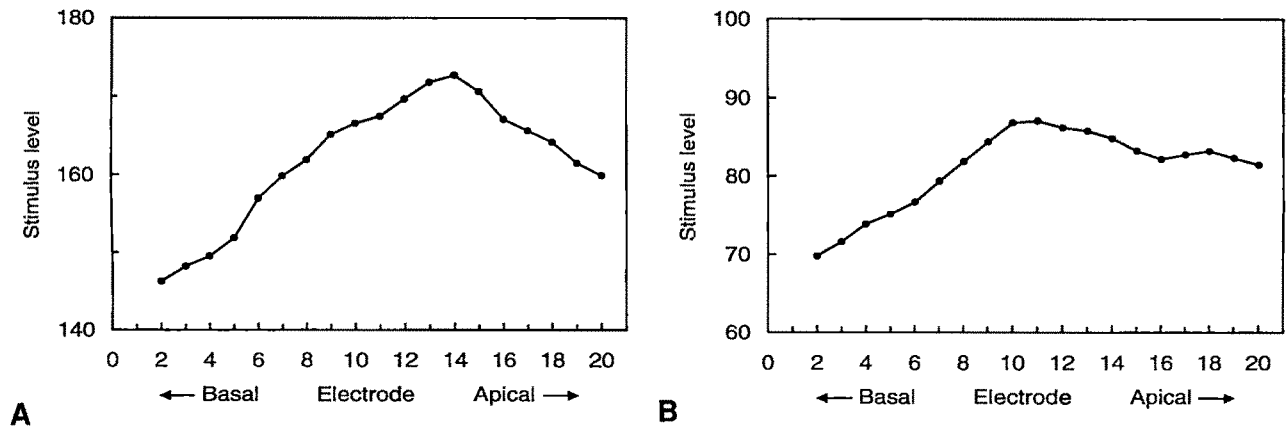


Fig 2. Figure 1 demonstrates that linear interpolation is not optimal. Here, templates are developed so that estimates can be adjusted for nonlinearities in maps. Average A) C levels and B) T levels were determined for this sample. These functions have been smoothed to reduce slight point-to-point irregularities. Clear departures from linearity are seen. These data are illustrative of this particular sample, and their use as norms might be inappropriate.

ample, if T levels were established for electrodes 1 and 6, there would be 4 interpolated electrodes — 2, 3, 4, and 5. This is termed 4-step linear interpolation.

For each patient, all data for electrodes 2 through 20 were used. Electrode 1 was not programmed in a sufficient number of patients for meaningful results, and electrode 20 is the highest available in BP + 1 mode. Step sizes from 1 to 10 were evaluated by means of all possible combinations. For example, step size 10 was implemented with electrodes 2 and 13 used as references, then electrodes 3 and 14, then 4 and 15, and up to 9 and 20. For each interpolated electrode at each step size, the mean error was determined.

Adjusted Maps. Linear interpolation, although easy to implement, may not be the best estimate of electrode sensitivity if the average maps deviate from straight lines. Therefore a strategy was evaluated in which the shape of the typical map was estimated, and this shape was used to adjust the interpolated map. Mean T and C levels were computed for this sample, and these means were used to adjust the estimated values. For example, if the T level for electrode 5 was being estimated from electrodes 2 and 13, the mean values for 2 and 13 were subtracted from the individual values before interpolation, and then the

mean value for electrode 5 was added to the result. The mean T and C levels were smoothed before the adjusted interpolations were performed. For example, the T level for electrode 3, T₃, in the smoothed function was set at $(T_2 + 2 \times T_3 + T_4)/4$.

RESULTS

Linear Interpolation. With linear interpolation, there was some imprecision in both T and C levels (Fig 1). The mean errors in levels — the difference between the average level and the average of the estimates — were modest for up to 5-step interpolation: less than 1 stimulus level for T levels, and less than 2 stimulus levels for C levels. With 10-step interpolation, the mean errors were as much as 4.5 and 9.5 stimulus levels for T and C levels, respectively.

Adjusted Maps. The mean errors are perhaps not unacceptable, but they can be eliminated by adjusting the interpolated values to take into account the nonlinearity of the average map. Figure 2 shows the average T and C levels for this sample, the functions being smoothed as described in Patients and Methods. Clear deviations from linearity are seen for both functions. Correcting for the nonlinearity in the average functions does not eliminate

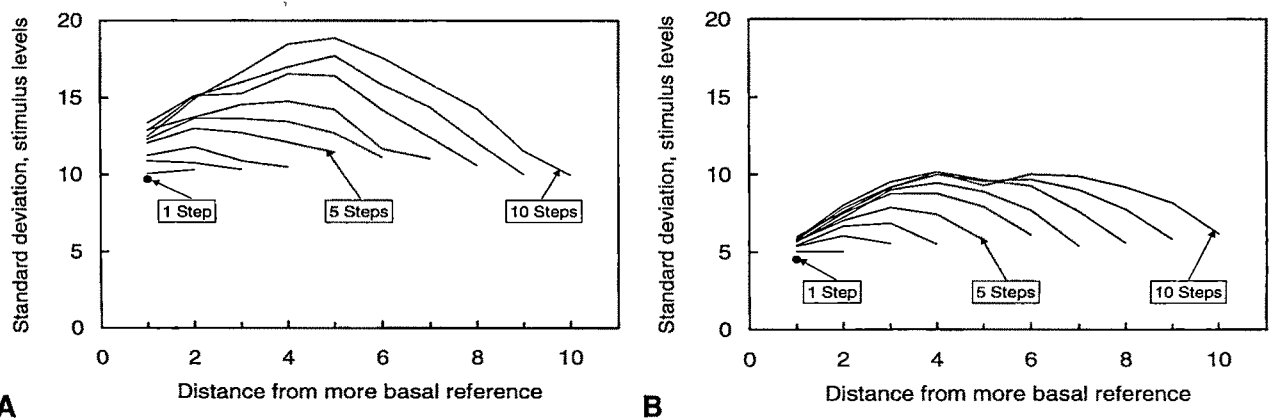


Fig 3. Use of functions in Fig 2 eliminates systematic bias seen in Fig 1, but there is considerable random variation in maps. Here, standard deviations of interpolation errors are shown for adjusted A) C levels and B) T levels. With 10-step interpolation, standard deviations are as great as 19 and 10 stimulus levels for C and T levels, respectively.

all sources of variation, however. Individual maps can have considerable variation from one electrode to the next, and much of this variation cannot be predicted from the average maps. Figure 3 shows the standard deviations of the discrepancies between interpolated and actual T and C levels. Even with 1-step interpolation, the standard deviations are 5 and 10 stimulus levels for T and C levels, respectively. With 10-step interpolation, the standard deviations are as much as 10 and 19 levels for T and C levels, respectively.

DISCUSSION

The precision of interpolation, even with adjustments for the shape of the typical map, is limited by certain factors. Implant users vary greatly in sensitivity and in the shapes of their maps.⁴ There is imprecision in determination of T and C levels, which would affect the interpolated values as well. Obviously, interpolation would require caution; the estimation of T levels would be crude and the estimation of C levels more so. The latter is of greater concern, because of the risk of discomfort during the child's early experience with the implant, and the

chance that an electrode might have a C level much below the estimated value. Even if estimation is used, it would seem imprudent to interpolate over many electrodes. With 10-step interpolation, for example, the error can be a large part of the dynamic range. Still, with conservative setting of the C levels, interpolation might enable the child to experience input from all electrodes early in the tuning process.

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COMMUNITY INVOLVEMENT IN COCHLEAR IMPLANTATION: DEVELOPMENT OF A COCHLEAR IMPLANT COMMUNITY COUNCIL

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The Nemours Children's Clinic Cochlear Implant Team created the Cochlear Implant Community Council (CICC) to provide a means to discuss issues of concern about pediatric cochlear implantation. The team recognized a specific need to increase understanding and mutual respect among members of the deaf community, the professionals involved with cochlear implantation, and the community at large through an exchange of knowledge about cochlear implants and deaf culture.

It was reasoned that a community council would provide a forum to discuss sensitive issues, to educate, and to provide accurate information regarding implantation, deafness, deaf culture, and education of deaf children, with specific attention to cochlear implantation. There were no expectations of changing individual beliefs; rather, the purpose was to understand and respect individual choices and points of view. The initial goal of the Council was to provide an avenue for the exchange of knowledge about cochlear implants and deaf culture as a means of facilitating understanding among all involved.

The Council comprises professionals from the cochlear implant team, deaf educators and administrators, deaf adults, hard-of-hearing adults, and a parent of a cochlear implant user. The following list describes the affiliations of the current Council members.

1. The mother of a cochlear implant user.
2. The Coordinator for Academic Advisement at the

Florida School for the Deaf and Blind.

3. The Administrator for the Deaf and Hard of Hearing Program for the Duval County Schools.
4. A professor of the Interpreter Training and Sign Language Program at The University of North Florida.
5. A supervising teacher at the Florida School for the Deaf and Blind.
6. The medical director of the Nemours Cochlear Implant Team.
7. A neurotologist-surgeon on the Cochlear Implant Team.
8. The coordinator of the Cochlear Implant Team.

The initial planning meeting of the CICC with all members was held in 1994. Members of the Council quickly realized that the first and most important goal was to define a mechanism for the exchange of accurate information about cochlear implants in children and about deaf culture. Quarterly meetings were scheduled. The formats for those meetings varied from closed sessions of concept- and information-sharing to open discussion groups with community members at large, program visitations, forums, presentations, panel discussions, and social events. Initially, the focus was on the technical aspects of the cochlear implant equipment, function, criteria, and evaluation and on techniques and issues of surgical implantation. Visits were made to the Nemours Children's Clinic and the facil-

ities for the cochlear implant program.

The Council goals for 1995 focused on the complexities and realities of being deaf and the deaf culture and on providing updated information regarding research and development trends in cochlear implantation. To start the year, the CICC and members of the cochlear implant teams from Nemours Children's Clinic and Mayo Clinic, Jacksonville, spent a day at the Florida School for the Deaf in St Augustine, Florida. The day's agenda included reports and discussions on "The Future of Cochlear Implants." The school staff was involved in presenting a mini-workshop on deaf culture. The initial goal of the Council was realized during this first year. Along with the exchange of accurate information about cochlear implants and the deaf culture came a new understanding of the sensitive issues.

The year 1996 saw an enthusiasm for the expansion of goals to include an interest in providing information to support an increased understanding of hearing loss and deafness and to investigate cochlear implant performance outcomes in children. The year's agenda included presentations and panel discussions on performance outcomes with case studies of children with cochlear implants included. The social events continued to provide an excellent forum for exchange of information and discussion of in-

dividual points of view among Council members and the community at large.

The development of the CICC has proved an effective concept to facilitate understanding and respect between the deaf and cochlear implant communities. Through a variety of educational formats, an exchange of accurate information regarding deaf culture and cochlear implantation has occurred.

Although each community has a different cultural understanding of the cochlear implant, the CICC has become a unique forum for discussing issues common to the deaf and hearing worlds. Through education, discussion, and open communication, increased understanding and respect among members of the Council have developed. This, in turn, has facilitated increased understanding and respect among families of deaf children, educators, professionals, and the deaf community at large. Ultimately, the ability of the CICC to address and listen to differing points of view has provided an important step in minimizing the sometimes adversarial relationship between the deaf and cochlear implant communities. This relationship is an important step in minimizing the negative effects of controversial issues about cochlear implantation on our pediatric patients and their families.

DEAF CULTURAL IDENTITY OF ADOLESCENTS WITH AND WITHOUT COCHLEAR IMPLANTS

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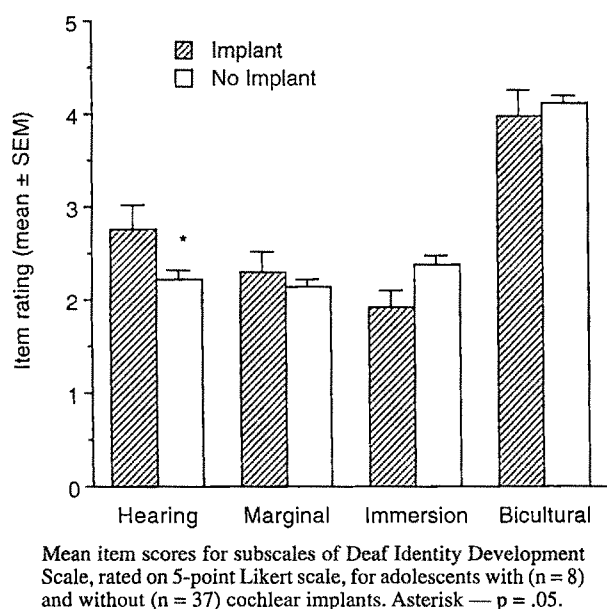
INTRODUCTION

Debates regarding pediatric cochlear implantation have once again raised the question of whether deafness should be considered a target for medical intervention or a cultural identity. Opponents of implantation argue that children with implants will be compromised as members of the deaf community and that their ability to develop a cultural identity will be impaired.^{1,2} This concern is predicated on the notion that deaf community membership protects against the social and emotional difficulties commonly associated with deafness.³⁻⁶

Deaf cultural identity is not solely based on hearing status.^{7,8} Cultural identity is usually conceptualized as "an organized set of self-perceptions and accompanying feelings that an individual has about her/himself with regard to some social category."^{9(p106)} Consistent with that conceptualization, Glickman and Carey⁴ offered a 4-category model of deaf cultural identity adapted from a model of racial identity.¹⁰ Members of the culturally "Hearing" category believe that deafness is pathological and that the deaf should strive to become as much like hearing people as possible. Accordingly, they value oral skills above manual communication skills. Individuals with a culturally "Mar-

ginal" identity feel alienated from both the deaf and hearing communities, falling somewhere between the two cultures and comfortable in neither. In "Immersion" identity, features of the deaf community (eg, American Sign Language) are exalted and uncritically embraced and efforts to approximate hearing (eg, lipreading, hearing aids, English-based manual communication) are denigrated. "Bicultural" identity reflects a balance between cultural pride in the deaf community and an appreciation of the positive aspects of the hearing culture. Persons with Bicultural identities have some degree of comfort and interactional skill in both deaf and hearing settings.⁴

Recently, researchers have attempted to establish links between the cultural identity of deaf persons and their psychological functioning. For example, in an indirect test, Bat-Chava¹¹ conducted a meta-analysis on the association of proxy measures of a Deaf identity (eg, having deaf parents, attending a residential school) with self-esteem. Although deaf subjects had lower self-esteem than hearing subjects, the proxy variables for a Deaf identity were associated with higher self-esteem. In a second study, Bat-Chava¹² found that self-esteem was lowest among the deaf who did not identify with Deaf culture. Studies that have



included a Bicultural identity category have produced somewhat different results. Weinberg and Sterritt¹³ reported that adolescents with a Bicultural identity had the best academic performance, had the most positive evaluation of themselves and their peer relationships, and were least likely to say that their families would love them more if they could hear. Deaf adolescents with a Hearing identity scored lowest on these measures of adjustment, while adolescents with a Deaf identity had intermediate scores. Cole and Edelman³ also reported that deaf adolescents with a Bicultural identity were rated as better-adjusted by their teachers.

The impact of cochlear implants on the cultural identity of adolescents is unknown. In many ways, cochlear implant users may be described as poised between the deaf and hearing worlds.² It is possible that such a position will facilitate the adoption of a Bicultural identity in which individuals are able to negotiate social interactions within both communities. Alternatively, cochlear implant users may feel alienated from both the deaf and hearing communities, ie, have a Marginal cultural identity.^{2,4} The primary goal of the present study was to examine the cultural identity of adolescent cochlear implant users in relation to deaf adolescents without cochlear implants. Because there have been no direct tests of the relation between deaf identity and social competence in deaf adolescents, the second goal of the study was to address this lack.

METHODS

Subjects. Forty-five deaf adolescents were recruited from 3 sources: a summer program for academically gifted deaf adolescents sponsored by the Boys Town National Research Hospital (BTNRH) in Omaha, Nebraska (12 boys, 6 girls); the Iowa School for the Deaf (ISD) in Council Bluffs, Iowa (16 boys, 6 girls); and The University of Iowa cochlear implant program (4 boys, 1 girl). The mean age of the sample was 14.5 (range, 12 to 18).

Measures. The Deaf Identity Development Scale

(DIDS⁴) is a 54-item questionnaire divided into 4 scales reflecting different deaf cultural identities: Hearing, Marginal, Immersion, or Bicultural. Items within scales are rated on a 5-point Likert scale.

Because the ISD and BTNRH participants were recruited from established peer groups, it was possible to obtain a measure of peer acceptance for this portion of the sample with the use of a standardized sociometric technique.¹⁴ The participants were presented with a class or group roster and instructed to select the 3 people with whom they most and least liked to spend time. The sums of each subject's positive and negative nominations were divided by the number of raters in the group.

The Teacher Rating Form (TRF¹⁵), a version of Achenbach's Child Behavior Checklist adapted for classroom use, was completed by a teacher knowledgeable about the participant's behavior. The TRF was scored to produce indices of internalizing and externalizing behavior problems.

Procedure. At BTNRH, the participants completed the DIDS and the sociometric questionnaire at the end of the 5-week summer program. The students at ISD completed the DIDS and the sociometric questionnaire late in the school year. In both settings, sign language interpreters were available to assist participants who might have difficulty reading the measures. The participants' teachers or resident advisors completed the TRF and returned it by mail.

The participants recruited from the University of Iowa were mailed the DIDS. The TRFs were obtained by mail from a teacher identified by the parent. It was not possible to administer the sociometric questionnaire to these participants, because of their wide geographic dispersal and the resulting lack of access to the subject's established peer groups.

RESULTS

Data Analysis. The participants with and without cochlear implants were compared on each of the 4 scales of the DIDS with *t*-tests. The relationships between the 4 DIDS scales and the measures of social competence were examined through correlational analyses. An α level of .05 was used for all statistical tests.

Deaf Identity and Cochlear Implant Use. The Figure shows the mean DIDS scale scores of the adolescents with and without cochlear implants. Both groups gave the most favorable ratings to items on the Bicultural scale. The cochlear implant users rated Hearing identity items significantly more favorably than did the adolescents without cochlear implants ($t(43) = 2.019$, $p = .050$). There was a tendency for the cochlear implant users to rate Immersion identity items less favorably than did the adolescents without implants; however, that difference was not statistically significant ($t(43) = -1.85$, $p = .071$). There were no significant differences between the two groups on the Marginal and Bicultural scales.

Deaf Identity and Social Competence. For the 37 participants who completed the sociometric measure, the scores

on the Marginal identity scale were significantly negatively correlated with positive peer nominations ($r = -.48$, $p = .049$). None of the DIDS scales predicted negative nominations from peers. Similarly, there were no statistically significant correlations between the TRF Externalizing and Internalizing scores and the DIDS scales.

DISCUSSION

In contrast to predictions by Deaf activists, this group of adolescents with and without cochlear implants had strikingly similar identity beliefs. Both groups indicated a high degree of approval of Bicultural identity statements, which reflect a balanced view of the hearing and deaf cultures. Although the sample was small, inspection of the data indicates that the absolute values and distributional characteristics for the DIDS scores of the two groups were highly similar on all scales except the Hearing identity scale. Because many implant users receive audiological benefit, it is not surprising that they describe emulating the hearing majority as a desirable goal.

Although it has been suggested that Hearing identity beliefs are indicative of problems for deaf people,^{3,11-13} in the present study, higher scores on the Hearing identity scale were not associated with teacher reports of social or emotional difficulties or with negative peer status. None of the previous studies that reported pernicious effects for a Hearing identity in deaf people included cochlear implant users. However, the present study also found no relationship between Hearing identity scale items and social competence in the deaf adolescents who had not received an implant. Therefore, the lack of an association cannot be attributed solely to audiological benefit from implant use.

The scores on the Marginal identity scale were negatively correlated with positive peer nominations. Because social isolation is central to Glickman and Carey's conceptualization of Marginal identity,⁴ the Marginal scale of the DIDS contains items directly reflective of problems with social relationships (eg, "It's hard for me to make friends"). Therefore it is not clear whether the beliefs reflected in the Marginal identity scale produce or merely reflect difficulties in peer relationships.

CONCLUSION

Contrary to assertions of deaf activists, deaf adolescents with cochlear implants endorse beliefs about deafness and Deaf culture that are similar to those of adolescents without cochlear implants. Moreover, Deaf cultural

identity appears to have little impact on social competence as assessed on the basis of teacher ratings or nominations by deaf peers. Importantly, the identity of deaf adolescents recruited from residential schools and other social contexts evidenced far more Bicultural identification, and far less immersion in the Deaf community, than would be expected on the basis of assertions by Deaf culture activists.

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EFFECTS OF COMMUNICATION MODE ON SKILLS OF LONG-TERM COCHLEAR IMPLANT USERS

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INTRODUCTION

An earlier longitudinal study comparing the progress of implant-fitted children with those fitted with hearing aids and tactile aids in a controlled and optimized educational setting indicated an overwhelming superiority of the cochlear implant for children with better-ear thresholds of greater than 100 dB.¹ A new study, recently undertaken by this group, is titled "Cochlear Implants and Education of the Deaf Child." This study is designed to hold the sensory aid constant (Nucleus 22-channel implant) and document the effects of various education and rehabilitation models on the deaf child's ability to understand, produce, and read English.

Although the eventual purpose of the study is to examine the impact of various combinations of rehabilitation settings on outcome measures while controlling for effects of intervening variables, this preliminary report on a partial sample is focused on effects of current communication mode (oral or total communication [TC]) on outcome measures. We have hypothesized that those children who rely on speech and hearing throughout the day for communication will develop higher levels of speech perception, speech production, language, and reading skills than children who rely on both speech and sign.

PARTICIPANTS

These 43 children were all 8- and 9-year-olds and had used implants for between 4 and 6 years. All children used the Nucleus 22 device: 33 with the SPECTRA processor (with the spectral peak [SPEAK] coding strategy) and 10 with the MSP processor (with the multiplex [MPEAK] coding strategy). They were enrolled in 37 public and 6 private educational programs located across the United States and Canada. Twenty-five were fully mainstreamed, 7 were partially mainstreamed, and 11 were in special education classes. All participants became deaf before age 3, resided in monolingual English-speaking homes, and had at least average nonverbal intelligence. Twenty of the children were enrolled in educational settings in which no sign was used (oral), and 23 children were in programs that used some form of manually coded English (TC). The oral and TC groups did not differ significantly in IQ, age at onset of deafness, duration of deafness, age at implantation, years of implant use, median family income, or median education of father. They did differ significantly in mother's education and number of hours of therapy received during the first 3 years after implantation. The oral group mothers averaged 4 years of college, and the TC group averaged 2 years. The oral group averaged 81 hours per year of therapy, whereas the TC group averaged 42 hours.

METHODS

All children completed a 6-hour battery of tests, administered over 3 days, to measure 4 outcome variables: speech perception, speech production, language, and reading. Representative tests were selected from the overall battery for this paper. The speech perception measures included perception of speech segments, closed-set word

identification, open-set word and sentence recognition, and visual enhancement of lipreading. All speech perception measures were administered with the use of recorded stimuli. The VIDSPAC (Video Speech Pattern Contrast test)² is a computer game that requires discrimination of specific phoneme contrasts involving consonant manner, place, voicing, and vowel cues. The child responds to a contrasting stimulus (eg, "sa") embedded in a repeated background (eg, "sha"). Two subtests of the Early Speech Perception (ESP) Test³ were administered: Spondees and Monosyllables. The child identifies words from a set of 12 pictures, primarily on the basis of vowel cues. The Word Intelligibility by Picture Identification (WIPI) test⁴ follows a similar procedure for word identification but uses stimulus contrasts that primarily require consonant recognition. Open-set speech perception was evaluated with tests that require the child to repeat the stimulus. The Lexical Neighborhood Test (LNT)⁵ consists of 50 monosyllabic words that have been selected to be within the vocabulary of young deaf children. A set of 16 Bamford-Kowal-Bench (BKB) sentences⁶ were scored on the basis of the child's recognition of 50 key words embedded in a simple sentence context.

The speech perception battery also included a measure of the amount of benefit to lipreading provided by the implant. The Children's Visual Enhancement (CHIVE) test⁷ contains lists of 20 words that are controlled for vocabulary level (words familiar to young children) and for visibility in a lipreading-only condition. Three recorded lists were presented on videotape: 1 in a lipreading-only condition, 1 in an audio-only condition, and 1 in an audiovisual condition.

In order to evaluate speech intelligibility, recordings of each child's production of the 32 McGarr sentences⁸ were played to 3 naive listeners, whose responses were scored in terms of the number of key words correctly identified. The receptive language measure used was the Test for Auditory Comprehension of Language (TACL).⁹ The TACL was administered individually in total communication. All children had the advantage of signed English input on this test to make iconic cues available equally to both groups.

Three standardized reading tests were administered. In the Word Attack subtest of the Woodcock Reading Mastery Test,¹⁰ the child must pronounce nonsense syllables from print, according to standard pronunciation guidelines. This test taps the child's ability to use phonological knowledge to decode new words. Two subtests of the Peabody Individual Achievement Test,¹¹ Recognition and Comprehension, were used to measure the child's sight vocabulary and sentence comprehension skills.

RESULTS

Average scores obtained by oral and TC groups are listed in the Table, along with results of *t*-tests examining the differences in mean scores. The VIDSPAC scores shown in the Table have been corrected for chance. The oral children demonstrated a significant advantage in their overall VIDSPAC score and in their discrimination of

MEAN AND STANDARD ERROR SCORES FOR CHILDREN ENROLLED IN ORAL (N = 20) AND TOTAL COMMUNICATION (N = 23) SETTINGS

		Oral		TC		p
		Mean	SE	Mean	SE	
Speech perception, percentage correct						
Segments, VIDSPAC	Total	71.5	3.2	52.8	6.9	.01
	Vowels	83.5	4.1	56.7	9.2	.01
	Voicing	55.6	4.3	53.2	7.1	
	Manner	88.4	3.9	59.4	8.6	.00
	Place	57.4	4.9	42.7	7.0	
Closed-set tasks	ESP Spondees	95.4	1.6	73.4	7.3	.00
	ESP Monosyllables	88.5	3.9	71.0	7.0	.03
	WIPI	56.7	4.4	39.6	4.8	.01
Open-set tasks	BKB Sentences	61.2	6.7	39.2	8.2	.04
	LNT Words	50.4	4.6	32.9	6.0	.02
CHIVE (visual enhancement)	Visual	41.5	3.8	38.5	4.2	
	Auditory	52.6	3.1	37.5	6.1	.03
	Auditory-visual	88.0	2.3	68.5	7.0	.01
Speech production, percentage intelligible						
Key words, McGarr Sentences	High context	84.4	4.3	57.0	8.6	.00
	Low context	70.8	5.7	46.9	7.8	.02
	Total	77.6	4.9	51.9	8.0	.01
Language, age scores in months						
TACL, simultaneous communication	Word classes	93.5	3.8	96.1	3.9	
	Grammatical morphemes	85.5	4.8	78.3	6.9	
	Elaborated sentences	76.0	5.4	80.0	6.8	
Reading grade equivalent scores						
Woodcock Word Attack	Grade score	2.9	0.2	2.3	0.3	
Peabody Individual Achievement Test	Word recognition	3.2	0.3	2.5	0.3	
	Comprehension	3.6	0.5	2.5	0.2	

manner and vowel cues. No difference was apparent in perception of voicing and place cues, which were difficult contrasts for both groups.

Significant differences between the oral and TC groups were apparent on all closed-set speech perception tests, with the oral children nearly topping out on the ESP and showing a 20% advantage on the WIPI test. Significant differences between groups were also observed on the open-set speech perception tasks. The oral children exhibited an average 20% advantage over the TC group on the monosyllable lists of the LNT and a 27% advantage on perception of key words in BKB sentences. The results indicate no significant difference between oral and TC groups in their lipreading-only performance on the CHIVE but indicate a significant advantage to the oral group in auditory and auditory-visual scores.

The speech production intelligibility scores also reflected a significant advantage for the oral students. In McGarr sentences with high contextual support, the oral children averaged 84% key words understood, compared with 54% for the TC group. In low-context sentences, the intelligibility of both groups dropped more than 10%, but the advantage to children from oral programs continued to be significant.

No significant differences were observed in average language and reading scores of the two groups. It had been

anticipated that TC children who used sign on a regular basis would benefit more than oral children from the use of sign on the receptive language test (TACL). However, the mean age equivalent scores of the two groups were quite similar on all 3 subtests. A comparison of reading grade equivalent scores indicated higher average scores for the oral group, but the differences did not reach statistical significance.

CONCLUSIONS

The ultimate purpose of this study is to describe the effect of various rehabilitation strategies on children's performance with multichannel cochlear implants. An analysis of how class placement, communication mode, speech therapy, auditory training, and parent involvement interact to optimize benefit from an implant will require analysis of the complete sample of 180 children, scheduled to be completed by the end of this study in 2001. These preliminary results indicate that students enrolled in educational settings in which they must depend on spoken language for communication achieve significantly more auditory benefit from an implant than do children whose program includes sign. This benefit is associated with greater speech intelligibility without any apparent decrement in receptive language skills from lack of exposure to sign language. The relative benefits of the two approaches for development of reading skills are equivocal

at this time and may become clearer as more children are added to the sample.

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WORKING MEMORY IN DEAF CHILDREN WITH COCHLEAR IMPLANTS: CORRELATIONS BETWEEN DIGIT SPAN AND MEASURES OF SPOKEN LANGUAGE PROCESSING

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INTRODUCTION

One of the most important problems in the field of pediatric cochlear implants is understanding the enormous individual differences in performance among children on a wide variety of outcome measures that assess speech perception, language comprehension, speech intelligibility, and reading. Some deaf children with cochlear implants do very well on standardized audiological and language tests and appear to be well on their way to acquiring spoken language through their implants, whereas other children do much more poorly and apparently never appear to reach these critical milestones in speech and language development.¹ What is the basis for these individual differences? Recent findings suggest that one factor may be related to the perceptual processing of spoken words, that is, the encoding, storage, and retrieval of the phonological representations of spoken words, and the use of working memory and rehearsal mechanisms.^{1,2} To examine the role of working memory in speech perception, word recognition, speech production, language, and reading tasks, we obtained auditory digit spans from 8- and 9-year-old prelingually deaf children who had used their implants for a period of at least 4 years, then computed correlations between digit span and 4 sets of outcome measures.

METHODS

Participants. The memory span data were collected by Geers et al from 43 prelingually deaf children who were between 8 years and 9 years 11 months of age as part of their study of long-term cochlear implant users (this supplement, pp 89-92). All children had used their cochlear implants for more than 4 years (mean, 5.5 years). Approximately half of the children were from oral-only programs, and half were from total communication (TC) programs.

The two groups did not differ significantly in IQ, age at onset of deafness, duration of deafness, age at implantation, or length of implant use. The two groups did differ in the number of hours of speech and language therapy they received during the first 3 years after implantation. The oral-only group received a mean of 81 hours of speech therapy per year, whereas the TC group received 42 hours.

Materials and Procedure. All children completed a 6-hour battery of tests distributed over 3 days to measure the 4 outcome variables: speech perception, speech production, language, and reading. The mean scores on these tests have been reported by Geers et al (this supplement, pp 89-92). In addition to this battery of tests, forward and backward auditory digit spans were also collected for each child by means of the digit span subtests of the Wechsler Intelligence Scale for Children (WISC-III).³ The digit spans were obtained by means of live-voice presentation at a rate of approximately one item per second with lip-reading cues available. The child was presented with a list of digits and was asked to recall the items on the list in the correct temporal order. Digit span was defined as the longest length sequence of digits that the child could recall correctly 2 times in a row.

RESULTS

Forward digit spans were correlated with the 4 sets of outcome measures obtained by Geers et al (this supplement, pp 89-92): speech perception, speech intelligibility, language, and reading. A summary of these correlations is displayed separately in the Table for each set of outcome measures.

Speech Perception. The simple correlations between digit span and the spoken word recognition measures were

CORRELATIONS WITH AUDITORY DIGIT SPAN

	<i>r</i>	<i>Partial r</i>
Speech perception		
Closed-set tasks		
WIPI	+ .71	+ .50
Open-set tasks		
LNT	+ .64	+ .37
BKB	+ .59	+ .28
Auditory + visual		
CHIVE	+ .66	+ .45
Speech production		
McGarr Sentences		
Transcription	+ .69	
Language		
WISC Similarities	+ .52	
TACL	+ .54	
Reading		
Woodcock Word Attack	+ .62	
PIAT		
Vocabulary	+ .59	
Comprehension	+ .41	
Rhyme	- .48	
WIPI — Word Intelligibility by Picture Identification, LNT — Lexical Neighborhood Test, BKB — Bamford-Kowal-Bench sentences, CHIVE — Children's Visual Enhancement test, PIAT — Peabody Individual Achievement Test.		

all positive and strong, especially for the closed-set WIPI test ($r = +.71$) and the open-set LNT ($r = +.64$), in which the words were presented in isolation. The correlation was also strong for words in Bamford-Kowal-Bench (BKB) sentences ($r = +.59$). Digit span was also positively correlated with the Children's Visual Enhancement test score ($r = +.66$), which measures the additional gain that lip-reading provides the listener over auditory-only presentation. Partial correlations were then computed with the variance from speech feature discrimination on the Video Speech Pattern Contrast test (VIDSPAC) removed. These partial correlations and total variance are also given in the Table. Except for the BKB, the partial correlations are still statistically significant, suggesting the presence of an independent source of variance associated with memory that is separate from audibility or speech feature discrimination.

Speech Production. The Table also shows the correlation of digit span with a measure of speech intelligibility obtained with the McGarr sentences. These sentences were presented to adult listeners who were asked to transcribe what they heard each child say. The simple correlation is +.69. The partial correlation with the VIDSPAC removed drops to +.48, but this still remains significant.

Language. The correlations of digit span with 2 language measures — the WISC-III Similarities Subtest, which measures vocabulary use and abstract reasoning, and the Test for Auditory Comprehension of Language, which measures receptive language comprehension — are also shown in the Table. Both correlations are positive and moderate, indicating a contribution of working memory to processing of spoken words and sentences.

Reading. Correlations of digit span and the 4 measures of reading performance are also given in the Table. Again, the correlations are moderate and statistically significant

for all 4 tests of reading.

DISCUSSION

The correlations between auditory digit span and the 4 sets of outcome measures obtained from these children suggest that some component of working memory plays an important role in mediating performance across a range of different tasks. Moreover, this component of memory contributes a common underlying source of variance to tasks that measure speech perception, speech production, language comprehension, and reading. The commonality among the processes used in these tasks appears to be related to phonological coding and rehearsal processes used to encode and retrieve the representations of spoken words from lexical memory. The differences in performance among cochlear implant users on these 4 outcome measures may reflect fundamental differences in the speed and efficiency of elementary information processing operations that are used in the encoding, rehearsal, retrieval, and manipulation of the phonological representations of spoken words.

The identification of working memory as the "locus" of the differences in performance between children with cochlear implants also suggests that what the child does centrally with the information received through a cochlear implant may be just as important as the nature of the sensory information and the initial neural representations of speech signals at the periphery. This account of the differences in performance not only explains the pattern of correlations of digit span with the language-based outcome measures, but also provides a processing mechanism that can be used to understand the effects of early auditory experience on development and the substantial effects of communication mode that Geers et al (this supplement, pp 89-92) found on almost all of the outcome measures. Oral-only children are not only exposed to more speech and language during their daily activities (see, for example, Hart and Risley⁴), but they are also engaged in more meaningful processing activities that require them to use spoken language to construct robust phonological representations of the sound patterns of words in their language.⁴

Taken together, our results suggest that spoken language processing and working memory are closely interconnected and share common reciprocal links, connections, and processing resources that are used in speech perception, speech production, language comprehension, and reading.

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LANGUAGE DEVELOPMENT IN CHILDREN FOLLOWING ONE YEAR OF CLARION IMPLANT USE

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INTRODUCTION

Improvement in auditory skill development in profoundly hearing-impaired children who receive multichannel cochlear implants is well documented in the literature. The impact of cochlear implants on communication skills, however, has been studied less extensively. Published reports¹⁻³ suggest that multichannel cochlear implants have a positive influence on the development of language skills. A recent study reported significant improvements in receptive and expressive language development in a group of young, prelingually deaf children implanted with the CLARION® Multi-Strategy™ Cochlear Implant after only 6 months of device use.⁴ The present study examined language changes that occurred in a subset of those children who had used their Clarion implants over a longer period (ie, 1 year).

METHODS

The subjects for this study were 18 prelingually deaf children implanted with the Clarion device at 2 investigational centers. All the children received some type of communication intervention, either privately or through their school, during the course of this study. The amount and quality of this intervention were assumed to vary across subjects but were not controlled for in this investigation. The mean age at time of implantation was 3 years 3 months (range, 2 years to 5 years 5 months). The mean preoperative unaided pure tone average (PTA) in the implanted ear was 111 dB hearing level (HL; range, 95 to 120).

The Reynell Developmental Language Scales-Revised (RDLS),⁵ a test standardized on children with normal hearing, was used to evaluate the receptive and expressive English-language skills of the children. The test was administered in each child's typical communication mode (ie, auditory-oral or total communication) before implant with hearing aids (PRE), and approximately 6 months (6M) and 12 months (12M) after surgery with the Clarion while using the Continuous Interleaved Sampler speech processing strategy.

Each child's raw score on the receptive and expressive sections of the RDLS was converted to a language age in months (ie, age equivalent score). Two methods were used to analyze the changes in age equivalent language scores that occurred after implantation. The first method involved comparison of the *absolute age equivalent scores* obtained at the PRE, 6M, and 12M intervals, averaged across all children. The second method measured the children's *rate of language growth* for receptive and expressive skills in the PRE and 12M, PRE and 6M, and 6M and 12M intervals. To calculate the rate of language growth, the change

in Reynell age equivalent score that occurred between the test intervals was divided by the time between intervals for each child, and then averaged across the 18 children. Calculations for the PRE intervals were based on the time of initial stimulation, given that our variable of interest was auditory stimulation provided by the implant. For example, a child who made 5 months of language growth in 6 months' time would achieve a growth rate of .83, or 83%. A growth rate of 6 months' language improvement in 6 months' time (ie, 1.0 or 100%) would indicate language growth equivalent to that of a child with normal hearing of the same language age.

RESULTS

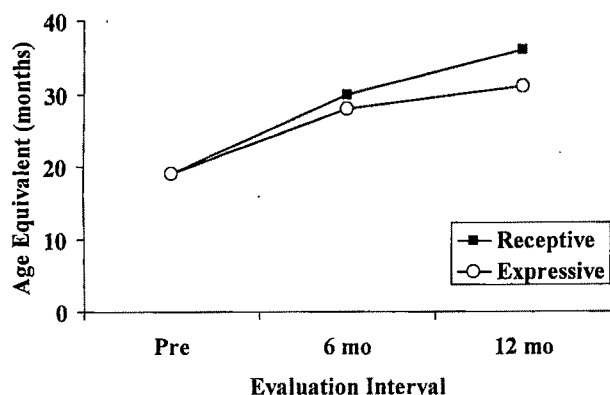
The Figure shows the mean age equivalent scores achieved by the 18 Clarion subjects at the PRE, 6M, and 12M intervals on the receptive and expressive portions of the RDLS. The results revealed a significant improvement in receptive and expressive language development between the PRE and 12M intervals ($p < .001$) and between the PRE and 6M and 6M and 12M intervals ($p < .04$). The mean receptive age equivalent score was 19 months at PRE (SD = 12), 30 months (SD = 14) at 6M, and 36 months (SD = 17) at 12M. The mean expressive age equivalent score was 19 months at PRE (SD = 11), 28 months (SD = 11) at 6M, and 31 months (SD = 13) at 12M.

The rates of language growth for receptive and expressive skills are shown in the Table. The growth rate expected for a child with normal hearing is 1.0, or 100%, corresponding to 6 months of language growth during a 6-month period (or 12 months of language growth during a 12-month period). The average rate of growth of receptive language skills during the entire 12-month period was 1.38, or 138%, indicating a faster rate of development than expected for children with normal hearing of the same language age. The data in the Table also show that the average rate of receptive language development was faster during the first 6 months of implant use (1.38 or 138%) than during the second 6 months of device use (1.10 or 110%).

The average rate of expressive language growth during the 12-month period was 0.98 or 98%, indicating approximately the same developmental rate expected for a child with normal hearing of the same language age. Again, the rate of expressive language change was substantially faster during the first 6 months of device use (ie, 1.40 or 140%) than during the second 6 months (ie, .51, or 51%).

DISCUSSION

The results of the present study show that both receptive and expressive language skills develop throughout



Mean age equivalent language scores on Reynell Developmental Language Scales-Revised for 18 prelingually deafened children at preoperative interval with hearing aids (Pre) and 6 and 12 months after implantation with Clarion cochlear implant.

the first 12 months of implant use. The rate of language learning was more accelerated during the first 6 months than during the second 6 months of implant use, especially for expressive skills. Because the children were so delayed in their language abilities at the time of implantation, rapid gains were more likely to occur during the first 6 months of device use, when testing occurred on linguistic tasks more appropriate for children of a much younger chronological age. As the children grow older and the gap closes between the children's language and chronological age, the test tasks become more difficult, slowing the apparent learning rate. Access to new sensory information through the use of a cochlear implant appears to bring about an acceleration in learning within the communication domain, as observed in these children during the first 6 months of device use. Developmental psychologists' notion of "equilibration," in which periods of accelerated growth in a cognitive skill are typically followed by less growth,⁶ may also help to explain the leveling-off of language learning in the second 6 months of implant use. Even with the marked improve-

RATE OF LANGUAGE GROWTH ON REYNELL DEVELOPMENTAL LANGUAGE SCALES FOR 18 CHILDREN IMPLANTED WITH CLARION COCHLEAR IMPLANT

	Preimplantation to 6 Months	Preimplantation to 12 Months	6 to 12 Months
Receptive language	1.62 ± 1.10	1.38 ± 0.81	1.10 ± 1.39
Expressive language	1.40 ± 1.10	0.98 ± 0.77	0.51 ± 1.06

Data are mean ± SD. Rate is expressed as proportion (change in age equivalent score divided by amount of time between intervals). Child with normal hearing is expected to demonstrate growth rate of 1.0 (6 months' increase in age equivalent score over 6 months' time).

ments observed in the language skills of the children in this study, the language levels of the implanted children remain delayed compared with those of their peers with normal hearing of the same chronological age, a finding also reported in other investigations.^{4,7} Further study of language development over a longer period is warranted, as well as investigations that identify the variables underlying individual differences in language development.

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USE OF FAST FORWARD™ TO ENHANCE LANGUAGE DEVELOPMENT IN CHILDREN WITH COCHLEAR IMPLANTS

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INTRODUCTION

Cochlear implantation has become an established option for (re)habilitation of profound deafness in children. Given uniform auditory thresholds after implantation, children still demonstrate a wide spectrum of performance in language acquisition and speech development, a finding that suggests that neural substrate differences and training effects underlie variable outcomes. Professionals working with children who have been fitted with implants must identify effective strategies for addressing the significant auditory perceptual, speech, and language needs of this

population.

We report our experience with a computer-based language-auditory skill training protocol (Fast ForWord™, Scientific Learning Corporation, Berkeley, Calif) with 11 children with cochlear implants. Fast ForWord™ strategies are based on observations, gleaned from assessment of temporal processing capabilities,¹ indicating that hearing children with language-learning impairments (LLI) require significantly longer interstimulus intervals to perceive and sequence 2 short-duration tones than do normal peer controls. Improvement in perceptual task per-

formance appears to result from intense practice with modified signals that incrementally approximate normal processing conditions.¹ Using common standardized measures of auditory and language skills, Tallal et al found that significant post-test gains were achieved in their initial trials² and for more than 300 children who completed the program at 35 field trial sites around the United States.^{2,3}

Fast ForWord™ was made available to licensed clinicians in January 1997 and has been used most extensively with LLI children. The program consists of 7 exercises in game format, each addressing an area of auditory or language skill. Children play five 20-minute games per day, 5 days a week, until a completion criterion is reached, usually around 8 weeks. Initially, stimuli are presented with significant reduction in formant transition speed and maximum highlighting of acoustic features of formant transitions. As the child's performance improves, processing demands are incrementally adjusted toward normal presentation. Subjects register their responses to challenging auditory tasks by using the mouse to select the correct picture in a 2-, 3-, or 4-item forced-choice model or by using the mouse to carry out directions or copy a sequence. Immediate feedback and virtual rewards for correct responses are provided, and items with incorrect responses are repeated with demonstration of correct answers. The games are designed to be entertaining and motivating while addressing the following skill areas: 1) imitation of a sequence of 2 pure tone sweeps, associated with shapes on the screen; 2) detection of a subtle consonant change in a string of consonant-vowel syllables; 3) matching a target syllable to 1 of 2 choices; 4) matching consonant-vowel and consonant-vowel-consonant syllables by remembering their placement in a grid of unrelated pictures; 5) following directions of increasing length and complexity involving size, shape, color, and position; 6) discrimination of pictured words differing by 1 phoneme; and 7) selection of pictures in response to sentences of increasing length and grammatic-syntactic complexity.

Our study was designed to address 2 questions: 1) Do children with cochlear implants have the auditory capability to perform the fine discrimination, memory, and comprehension tasks presented through computer-generated, temporally altered signals? and 2) will intense training and incremental increases in processing demand produce benefits in real-time language and auditory skills for the cochlear implant population?

SUBJECTS AND METHODS

We studied 11 children who received cochlear implants at Johns Hopkins and were either currently or previously enrolled in our rehabilitation program. These subjects represented a heterogeneous group in terms of history and functional communication skills. Their average age was 7 years 6 months (range, 4 years 10 months to 11 years 5 months), and average length of implant experience was 2 years 5 months (range, 6 months to 5 years). Two subjects used the Clarion device, and 9 used the Nucleus 22. Communication mode and school placement varied (5 to-

tal communication; 2 cued speech, 4 oral). All of the children were familiar with the clinical setting and staff and were judged to possess the attention and cognitive abilities necessary to understand the tasks of Fast ForWord™. The subjects displayed no significant handicapping conditions other than language and auditory processing deficits associated with their hearing loss. The conduct of the study was in compliance with the regulations of the Johns Hopkins University Joint Committee on Clinical Investigation.

The Fast ForWord™ program was presented without modification for the implant population, with the exception of signal delivery: since use of headphones was not possible, we used custom-designed patch cords (Audiovisual Systems, Baltimore, Md) to couple the speech processor directly to the audio output port of the computer (Macintosh 6400). The cords electrically isolate the implant and eliminate background noise. Trained adult monitors provided encouragement and supervision to enhance compliance, but no substantive assistance was given.

Pretraining. The general skills needed to engage in the Fast ForWord™ games include knowledge of the concepts *same*, *different*, *match*, *change*, *circle*, *square*, *large*, and *small*; the ability to use the mouse; and comprehension of 5 color labels. The subjects were briefly instructed in these areas as needed before beginning play.

Test Protocol. Performance was assessed with the use of repeated standardized measures commonly used by speech-language pathologists. All tests were administered according to the standard procedures designated in the manuals. Sign language or cued speech was used during testing only as needed to clarify instructions and provide encouragement. The children's signed or cued responses were accepted if appropriate to the task. The examiner's face was visible to the child during all tests except the Test of Auditory Perceptual Skills-Revised (TAPS-R) Word Discrimination subtest.

The following tests were used to measure performance in auditory memory, discrimination, receptive and expressive grammar and syntax, and phonological awareness: 1) the Clinical Evaluation of Language Fundamentals-Preschool (CELF-Pre)⁴, a comprehensive battery testing varied components of receptive and expressive language for children ages 3 years to 6 years 11 months; 2) the Clinical Evaluation of Language Fundamentals-3 (CELF-3)⁵, a comprehensive receptive-expressive battery for ages 6 years to 21 years 11 months; 3) the Test of Auditory Perceptual Skills-Revised (TAPS-R)⁶, an assessment of auditory memory for varied stimuli and open-set auditory word discrimination; 4) the Token Test for Children⁷, following directions of increasing length and complexity involving a limited lexical set; 5) the Assessment of Children's Language Comprehension (ACLC)⁸, picture selection based on increasing number of critical linguistic elements; 6) and the Phonological Awareness Test (PhAT)⁹, assessment of segmentation, blending, rhyming, and association skills given auditory stimuli.

The Token Test for Children closely resembles the items

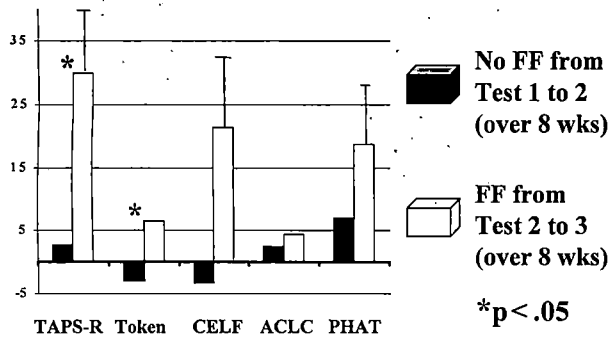


Fig 1. Comparison of mean changes in raw scores for 5 measures under no-Fast ForWord™ (no FF) condition and Fast ForWord™ (FF) condition. See text for abbreviations of test names.

presented in one of the Fast ForWord™ exercises (Block Commander). The other tests used, however, are general skill assessments that do not employ any items practiced during Fast ForWord™. The format, stimuli, and response modes are unrelated to those incorporated in the Fast ForWord™ exercises.

Crossover Design. Four subjects were tested 3 times, at 8-week intervals, and trained with Fast ForWord™ during the second 8-week period. We compared the changes in test results during these equivalent time spans. The remaining subjects were tested before and after Fast ForWord™ only. For children with 3 sets of scores, the higher of the 2 pretest levels was included in the group data.

Analysis of test results yielded raw scores, standard scores, and (for the CELF) age equivalencies. For CELF data, the Predicted Developmental Rate (PDR)¹⁰ was used to compare observed test score gains with those expected to occur with maturation. For all tests, changes in raw score and standard score for individual subjects, and changes in group means were also compared.

RESULTS

The first set of results involved the 4 subjects who were tested 3 times under the single crossover model. The mean differences between raw score 1 and raw score 2 (no Fast ForWord™ condition) and between raw score 2 and raw score 3 (Fast ForWord™ condition) are illustrated in Fig 1. Performance under the Fast ForWord™ condition was significantly higher on the TAPS-R and Token Test ($p <$

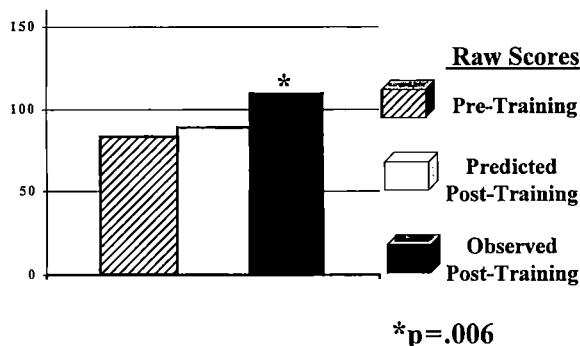


Fig 3. Comparison of mean raw score change on CELF with changes predicted from maturation alone.

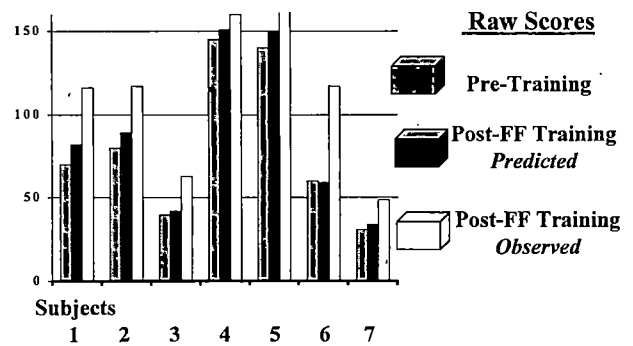


Fig 2. Pre-FF, predicted post-FF, and observed post-FF changes on CELF raw scores. All subjects exceeded gains expected from maturation alone.

.05) and was consistently improved on the other tests as well.

Next, predicted and observed changes were calculated for 7 subjects who were given the complete CELF. Pre-test language quotients were calculated by dividing language age by chronological age, and the resulting figure was used as the PDR for that child. The predicted language age at post-testing was determined by multiplying the post-test chronological age by the PDR. The maximum expected raw score was then determined from tables of test norms. Each subject's observed raw score exceeded the predicted level (Fig 2). Group mean score changes (Fig 3) were significant ($p = .006$).

Figure 4 illustrates pretest and post-test results for the entire subject cohort for the CELF, TAPS-R, ACLC, and PHAT. The subjects showed significant improvement on all tests ($p < .05$) after 8 weeks of Fast ForWord™ training. The standard score changes were also significant ($p < .05$).

In addition to objective measures, the parents were asked to complete a 45-item survey of perceived changes in communication skills after the training. The survey items dealt with receptive, expressive, and pragmatic language skills. The total number of responses in each rating category is illustrated in Fig 5. Improvement was noted on 83% of the survey items ($n = 7$), although "marked" changes in particular skills accounted for only 5% of the responses.

DISCUSSION

Conversational speech comprises a stream of acoustic

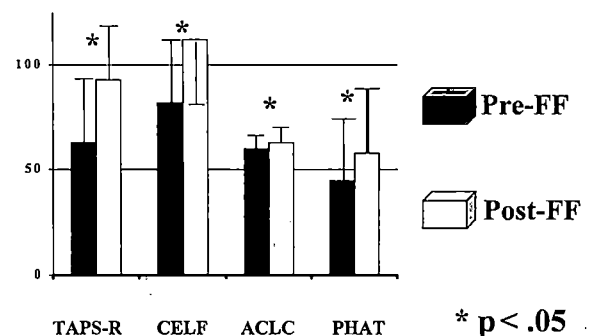


Fig 4. Pre- and post-FF test results on indicated tests. Raw scores are illustrated; standard score differences were also significant.

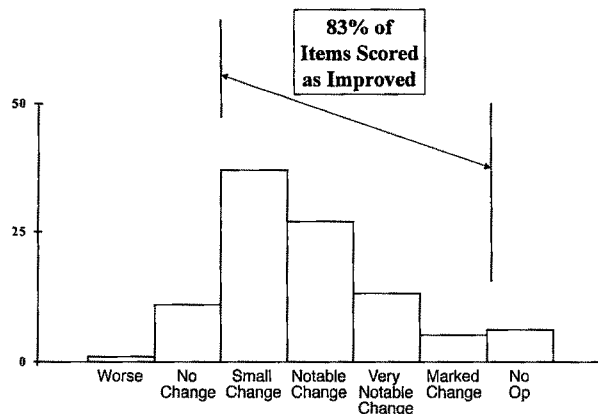


Fig 5. Parental rating scale completed following FF training. Scale consisted of 45 items covering receptive, expressive, and pragmatic language skills.

events that normal listeners segment and interpret with ease. Sequential acoustic signals are characterized by rapid transitions in formant frequency reflecting modifications in the shape of the vocal tract as phonemes are co-articulated. Formant transitions constitute important cues for identifying phonemes, particularly stop consonants and affricates.¹¹ Fast ForWord™ presents auditory signals that are parametrically altered by changes in the rate of formant transitions and by acoustic enhancement of transitions. One factor that may underlie the observed gains is that training with Fast ForWord™ improves subjects' ability to perceive, sequence, and interpret formant transitions.

In addition to qualitative changes in stimuli, a major component of the Fast ForWord™ training paradigm lies in its practice intensity. Fast ForWord™ provides children with more than 1,000 consistent, structured, and incrementally modified auditory stimuli during each daily session, a model that cannot be replicated in traditional intervention. Only computer-based strategies can offer this density of auditory stimuli, which may be critical to the gains observed.

The structure of Fast ForWord™ resembles normal language acquisition in that it addresses learning from a gestalt, or top-down, perspective (practice with syllables, words, and connected language) and, simultaneously, from an elemental, "bottom-up" perspective (temporal alteration and acoustic enhancement of formant transitions). It is not possible to draw conclusions concerning the relative importance of these components in the observed outcome. However, it appears that this intervention strategy as a whole can produce measurable progress over a relatively short period and may provide a beneficial adjunct to traditional therapy. The characteristics of Fast ForWord™ — intersession consistency, signal modification, and intense repetition — do not provide exposure to the interpersonal language exchanges that nurture optimal communication skills. Long-term follow-up will examine the durability of observed gains and the future language-learning curve of our subjects. Fast ForWord™ may allow children to derive increased benefit from subsequent intervention and incidental learning opportunities. It is important to note, however, that even with the benefits of

Fast ForWord™ and cochlear implantation, most of our subjects remained below the normal language levels for their chronological ages (compared with hearing peers). Before Fast ForWord™, the mean delay on the CELF was 33.1 months (SD, 24.9; range, 9 to 76 months). After Fast ForWord™, the mean delay was 24.6 months (SD, 23.2; range, 0 to 58 months). The difference between these degrees of delay compared with chronological age at the time of testing was significant ($p = .003$), and delays remained for all but 1 of our subjects.

CONCLUSIONS

Our results indicate that children with cochlear implants can perform the auditory perceptual and linguistic tasks of the Fast ForWord™ program. Our subjects showed consistent post-test benefit on 5 standardized measures of language and auditory processing abilities. The degree and distribution of gain varied among subjects, and no correlations with any of the demographic characteristics of our sample were found. Children who use total communication benefited as much as those using oral or cued speech methodologies, even though auditory skills only were practiced through experience with Fast ForWord™. The preliminary evidence presented here suggests that specialized training of linguistic and perceptual tasks may provide an avenue for enhancing receptive and expressive communication skills.

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LANGUAGE DEVELOPMENT IN CHILDREN WITH PROFOUND AND PRELINGUAL HEARING LOSS, WITHOUT COCHLEAR IMPLANTS

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INTRODUCTION

Most children who are born profoundly deaf, or who become deaf before the age of 3, fall significantly behind their hearing peers in their mastery of the surrounding oral language in all its forms: written, read, spoken, and signed. Published reports of English-language achievement in this population document significant delays in all language domains, regardless of whether the profoundly deaf children used oral communication (OC, which excludes the use of manual signs) or total communication (TC, the simultaneous use of oral and manual language).¹⁻⁵ It is not surprising, then, that a study of Stanford Achievement Test–Reading Comprehension scores in students with hearing impairment, between the ages of 8 and 18 years, who receive special services in schools throughout the United States showed median reading comprehension levels below those of average normal-hearing third graders.⁶

The development of an oral language is one of the most important potential outcomes of clinical interventions designed to restore hearing to children with profound hearing loss. In particular, both proponents and opponents of cochlear implantation in children agree that one important measure of the efficacy of this technology is whether it enhances the development of an oral language. However, it is not sufficient simply to document improvement in English-language abilities by cochlear implant users, because even children with profound hearing loss who do not have cochlear implants show a limited amount of improvement in English-language abilities over time. Previous studies have used different approaches to estimate the amount of language development to be expected from profoundly deaf children with cochlear implants.⁷⁻⁹ This study investigated the effect of several variables on the language development of children with profound and prelingual hearing loss who did not have cochlear implants, in order to generate a predictive model that could be used to estimate the improvements due to maturation and training. This model provides a useful benchmark that future studies will employ to determine whether the effect of cochlear implantation on language development exceeds the change in language development that would be expected from maturation and training alone.

METHODS

Participants. The participants were 113 children with profound, prelingual hearing impairment, ranging in age from 16 to 106 months (mean, 48 months). All had experienced onset of profound hearing loss before the age of 3 years (mean age at onset, 5 months); 81 subjects were congenitally deafened, whereas 32 of the children were

deafened between birth and 2 years 11 months of age. All children wore either a hearing aid or a tactile aid and were audiotically suited to a cochlear implant. The average age at aid fitting was 18 months, so the average time of total acoustic deprivation was 13 months. Sixty-seven of the subjects used TC, and 46 used OC. There were 17 children with pure tone averages (PTAs) between 90 and 100 dB hearing level (HL), 25 with PTAs greater than 100 but less than or equal to 110 dB HL, and 71 with PTAs greater than 110 dB HL. Most children in the sample received a cochlear implant after being tested, and 20 of the children have not received an implant.

Testing. Language development was assessed with the expressive section of the Reynell Language Development Scales.¹⁰ The test was administered in the child's preferred modality of English: either TC or OC. This test has 3 components: *structure*, which assesses the complexity of expressive language, from prelinguistic vocalizations to the use of complex sentences; *vocabulary*, which assesses the child's ability to name objects and pictures as well as to describe internalized concepts; and *content*, which assesses the more creative uses of language. The raw scores were converted to a language age score (in months) based on normative data from 1,319 children with normal hearing.¹⁰

Statistical Analysis. Several linear and nonlinear regressions were performed with the age-equivalent scores from the Reynell scales as the dependent variable and different combinations of the following independent variables: age at testing, communication mode (OC or TC), time of auditory deprivation, age at onset of profound deafness, and amount of residual hearing. This last variable was implemented in 2 different ways: as a continuous variable, measured as the PTA in dB HL at 0.5, 1, and 2 kHz, and as a discrete variable assuming 2 possible levels, one for PTAs between 90 and 100 dB HL and a second level for PTAs greater than 100 dB HL.

RESULTS

The regression analyses revealed that the age-equivalent language scores were strongly dependent on age at the time of testing. Age at onset of profound hearing loss and time of auditory deprivation did not have an influence on the language scores, perhaps because of the limited range of these variables in the data set. Communication mode and residual hearing did have an influence on the language scores, but to a lesser extent than the "age at testing" variable. The "residual hearing" variable had more explanatory power when it was encoded as a discrete variable than when it was encoded as a continuous variable. The regression function that provided the best fit to the

TABLE 1. REGRESSION RESULTS

Parameter	Coefficient	p
Intercept	1.927	.294
Slope	0.377	<.001
Slopediff1	0.0334	.233
Slopediff2	0.0940	.011

data was Expressive language score = intercept + age $\times$ (slope + slopediff1 $\times$ mode + slopediff2 $\times$ sb), where "mode" assumed values of 0 or 1 depending on whether the child used TC or OC, and "sb" assumed values of 0 or 1 depending on whether the PTA was greater than 100 dB HL or in the 90 to 100 dB HL range, respectively. Given this regression function, the "slope" variable is the best estimate of the improvement over time to be expected from children with profound prelingual hearing impairment, with a PTA greater than 100 dB HL and who use TC. "Slopediff1" is the best estimate of how much steeper the improvement slope is for children who use OC than for those using TC. Finally, "slopediff2" is the best estimate of how much steeper the improvement slope is for children who have PTAs between 90 and 100 dB HL than for children with PTAs greater than 100 dB HL. The adjusted r^2 of this regression (ie, the percentage of the variance explained by the regression) was 59%. Other results of this regression are listed in Table 1. When a linear regression of language score as a function of age at testing was performed (disregarding all other possible independent variables), the adjusted r^2 was 52%.

DISCUSSION

Table 2 shows the estimated slopes of language growth over time for each subgroup of children in this study. The fact that all these estimated slopes are less than or equal to 0.5 indicates that all these groups of children would be predicted to increase their expressive language skills at less than half the rate of their hearing peers. It must be remembered that these results are valid for oral language only, in which children with profound hearing loss are at a disadvantage. The present results provide a benchmark that may be used in future studies to show the efficacy of various interventions intended to improve oral language skills in children with profound hearing loss. In addition,

TABLE 2. ESTIMATED SLOPES OF EXPRESSIVE LANGUAGE GROWTH FOR EACH SUBGROUP OF CHILDREN

Subgroup	Slope
TC, PTA >100 dB HL	0.38
OC, PTA >100 dB HL	0.41
TC, PTA 90-100 dB HL	0.47
OC, PTA 90-100 dB HL	0.50

TC — total communication, PTA — pure tone average, HL — hearing level, OC — oral communication.

these results suggest that proper identification and management of early profound hearing loss is desirable not only from the point of view of perceptual benefit, but also because of the possible effect on oral language development.

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PSYCHOLOGICAL PREDICTORS OF PEDIATRIC COCHLEAR IMPLANT USE AND BENEFIT

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INTRODUCTION

The audiological outcome of pediatric cochlear implantation is highly variable.¹⁻⁴ Identification of the sources of this variability would greatly improve the ability of parents to make an informed decision as they consider cochlear implantation for their child. Additionally, knowl-

edge of contributors to variability could aid clinicians in helping patients attain maximal audiological benefit from the device. Although past work has shown that variability can be related to demographic characteristics, such as age at implantation,⁵⁻⁷ the amount of variance accounted for by demographic variables is modest. Thus, current

knowledge of predictors of outcome variability remains incomplete.

The importance of predicting implant use before attempting to predict implant benefit is indicated by several lines of evidence. First, long-term implant benefit has been correlated with use of implants during the initial period following connection,^{8,9} as well as with hours of implant use per day.⁵ Second, a link between experience with the implant and audiological benefit has been established.¹⁻⁴ Beyond the fact that implant use is a prerequisite for audiological benefit, other studies have reported discontinuation of implant use by pediatric recipients who likely terminated use before significant benefit could be achieved.¹⁰ In short, it is critical to be able to predict use of an implant before attempting to isolate other contributors to audiological variability.

Parenting is a probable contributor to implant utilization. The speech processor of a cochlear implant must be maintained and worn if the user is to perceive acoustic events. For young children, the effective daily use of the processor depends on the actions of parents. As a result, the degree to which parents ensure implant use is hypothesized to contribute to audiological benefit. Additionally, if parents have difficulty managing their children's behavior, they may be unable to ensure implant use. Therefore, the current study was designed to determine whether indices of parent and child behavior predict implant use and audiological outcomes among pediatric cochlear implant recipients.

METHODS

Subjects. The participants were 69 (33 boys) consecutive implant recipients, who were enrolled in a cochlear implant research protocol at the University of Iowa and had 36-month follow-up data. To receive an implant in this protocol, the children had to evince a prelingual (prior to 18 months of age), profound, bilateral deafness (≤ 95 dB hearing level) and receive no significant benefit from hearing aid use. Exclusionary criteria included only factors that could limit compliance with the established protocol (eg, illiteracy, severe parental psychopathology) and factors that could confound measured outcome variables (eg, retardation). With monetary support available to defray the cost of implantation, the sample was unrestricted by economic factors.

Procedure. Psychological evaluations were part of a multidisciplinary evaluation conducted over the course of several days (no more than 3 months) before implant surgery. The preimplant psychological evaluation was typically scheduled after the implant candidates had met the audiological, medical, and radiological criteria for implant eligibility. This assessment included a number of procedures (eg, diagnostic interviews, videotaped direct observations of family interaction) not analyzed in the current study. For most subjects, the psychological tests were administered during 1 full day of testing, with the aid of a sign language interpreter. Annual follow-up sessions were scheduled for both psychological assessments and tests of audiological function.

Psychological Measures. The focal measures of the

present study included 3 standardized questionnaires completed by the child's parents. The Child Behavior Checklist (CBCL)¹¹ is a standardized measure with established reliability and validity that is widely used for assessing a range of deviant and maladaptive behaviors, as well as composite Internalizing and Externalizing behavior problem scores. The Missouri Children's Behavior Checklist (MCBC)¹² is a second parent rating of child behavior that includes scales that are not redundant with the CBCL. The Home Environment Questionnaire (HEQ)^{13,14} is a true-false questionnaire that obtains objective information about the child's environment from the child's mother. The HEQ has 8 empirically derived scales measuring specific dimensions of a child's psychosocial environment that are theoretically important for the expression of deviant and nondeviant child behaviors.¹⁵ Together, these instruments provide information directly related to child sociability and parent-child interactions.

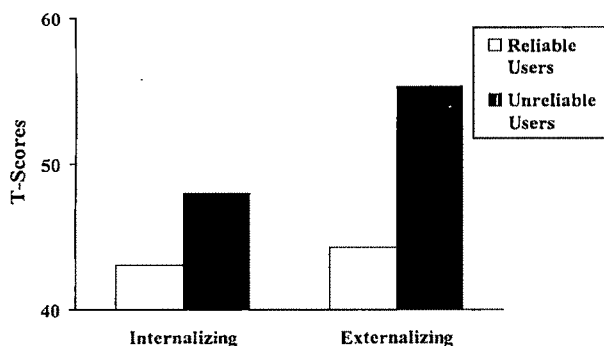
Two measures of general intelligence that require no verbal communication were also administered before implantation. The Leiter International Performance Scale (Leiter)¹⁶ is a widely used measure of nonverbal intelligence, and the Hiskey-Nebraska Test of Learning Aptitude (Hiskey)¹⁷ is a test designed to assess intelligence in hearing-impaired populations.

So that they could provide information regarding daily implant use, the parents were telephoned on 5 consecutive evenings at quarterly intervals and administered a standardized set of questions following the Parental Daily Report (PDR) paradigm.¹⁸ The audiological test battery administered at annual follow-up sessions included the Monosyllable-Trochee-Spondee test (MTS), the Word Intelligibility by Picture Identification test (WIPI), the Phonetically Balanced-Kindergarten (PBK) word lists, a vowel recognition measure based on a 4-choice monosyllable test, and a consonants recognition measure derived from both the Central Institute for the Deaf 4-choice Spondee list and the 4-choice Monosyllable test.

RESULTS

On the basis of the report of attending audiologists, 55 children (26 boys and 29 girls; mean age at implantation, 5.3 years; range, 2 to 13 years) were categorized as "reliable" implant users. Fourteen children (7 boys and 7 girls; mean age at implantation, 8.3; range, 2 to 15 years) were characterized as either "unreliable" users or "nonusers." Reliable users were reported to wear the processor at home and outside the home during most waking hours. In contrast, nonusers ceased processor use within 12 months of connection, and unreliable users wore the processor rarely (eg, only at school), and their devices were often poorly maintained (eg, frequent dead batteries). For the purpose of analyses, nonusers and unreliable users were combined into the "unreliable group" for comparison with the "reliable group."

Predicting Implant Use. In terms of demographic characteristics, the results indicated that the reliable group was significantly younger than the unreliable group ($t = 2.61$, $p < .05$). The reliable and unreliable groups did not differ with respect to the mean Leiter and Hiskey-Nebraska IQ



Mean Child Behavior Checklist "internalizing" and "externalizing" scores of "reliable" and "unreliable" user groups obtained from children's mothers before implantation.

scores. As shown in the Figure, the reliable group evidenced significantly fewer "externalizing" behavior problems on the preimplant CBCL ($t = 2.75$, $p < .05$). Thus, the mothers of the unreliable group reported a general pattern of difficulty with their children before implantation that reflected child externalizing problems (eg, non-compliance, destructive behavior, and attention problems).

To further investigate the predictability of implant use, we correlated the overall mean daily hours of implant use, obtained quarterly with the PDR, with preimplant psychological variables. The overall hours of use correlated significantly with the HEQ Affiliation ($r = .41$, $p < .05$), Sociability ($r = .49$, $p < .01$), and Social Status ($r = .39$, $p < .05$) scales. Consistent with these HEQ measures of intra-familial sociability, the child sociability measure (MCBC Sociability Scale) correlated with hours of use ($r = .40$, $p < .05$). In addition, the CBCL Anxious/Depressed Scale correlated negatively with hours of use ($r = -.63$, $p < .005$). This pattern of significant correlations indicates that mothers who described their children and homes as more sociable and affiliative before implantation tended to have children who used the implant more during the 36 months after surgery. The mothers of better users were also less likely to characterize their children as anxious or depressed before implantation.

Predicting Audiological Benefit. Because the unreliable group did not provide a full complement of audiological scores after implantation, correlations between preimplant measures and audiological measures were conducted with the reliable group only. For these correlations, distribution and scatterplots were examined to ensure the findings would not be compromised by the contribution of influential outliers. None of the correlations between the preimplant Hiskey and Leiter scores and the audiological follow-up scores approached statistical significance, a finding indicating that general tests of intelligence did not predict audiological benefit.

A somewhat different pattern of correlations was obtained with the parent ratings on the CBCL. The Table shows the correlations between the audiological measures at each follow-up and the preimplant CBCL Internalizing and Externalizing scores. With correlations ranging from $-.56$ to $+.22$, the overall pattern of correlations between the preimplant CBCL Internalizing scores and the postim-

CORRELATIONS BETWEEN PREIMPLANT MATERNAL CBCL COMPOSITE SCORES AND AUDIOLOGICAL FOLLOW-UP SCORES

	Internalizing			Externalizing		
	12 mo	24 mo	36 mo	12 mo	24 mo	36 mo
MTS-Stress	.10	.15	-.05	-.09	-.21	-.25
COMW	.22	-.11	-.16	-.17	-.43*	-.23
Vowel features	-.31*	-.17	-.27	-.17	-.32	-.33
MTS-Words	-.23	-.15	-.27	-.13	-.33	-.39
WIPI	.20	-.10	-.36	-.19	-.43*	-.34
PBK-Phonemes	.17	-.02	-.53†	-.13	-.37	-.41
PBK-Words	.07	-.05	-.56†	-.12	-.27	-.32

COMW — Combined 4-Choice Spondee and 4 Choice Monosyllable Test, WIPI — Word Intelligibility by Picture Identification Test.

* $p < .05$.

† $p < .01$.

plant audiological scores suggests that there is no systematic relationship between implant benefit and maternal reports of internalizing behavior problems. The CBCL Externalizing score did not significantly predict audiological scores at the 12-month follow-up, yet the pattern of correlations based on the 24- and 36-month follow-ups was dramatically different. Although not all correlations were statistically significant, they all approached significance, and they were all negative and of the same relative magnitude. Thus, unlike other psychological measures, the maternal ratings of externalizing behavior before implantation accounted for at least 10% of the variance in 10 of 14 audiological scores 2 or 3 years after implantation.

DISCUSSION

Because unreliable use was identified long before significant audiological benefit was likely to be realized, unreliable use is not attributable to limited audiological benefit. The contrasts between reliable and unreliable groups, as well as correlational analyses, suggest that children who are viewed by mothers as sociable and low on externalizing problems before implantation use their implants more consistently. In addition to the association between externalizing behavior and implant use, preimplantation externalizing behavior was negatively related to audiological outcomes at both the 24- and 36-month follow-ups. The absolute magnitude of these correlations is modest, accounting for no more than 17% of the variance in audiological outcomes, and often only approaching statistical significance. It is important to note, however, that the correlations were based on a severely truncated range of scores, which should greatly reduce obtained correlations. That is, because the nonusers had higher levels of externalizing behavior and would necessarily have low audiological scores (0 or chance), the absence of nonusers from the correlational analyses essentially eliminated most subjects from 1 quadrant of the scatterplot. This truncated range of predictors and outcomes, along with the benefit of multi-method assessment (ie, no shared method and source variance across measures), supports the importance of the obtained correlations well beyond their level of significance. Indeed, it is probable that the relationship between preimplant externalizing behavior and implant ben-

efit is even stronger than that reflected in the obtained correlations.

The striking consistency of the relationship between the preimplantation maternal reports of externalizing behavior and the implant outcomes is underscored by the fact that measures of positive social behavior (eg, sociability, affiliation) are related to reliable implant use. More sociable children may have more opportunities to use the implant and may also experience more social reinforcement for engaging in efforts at communicating.

CONCLUSION

This study provides evidence that psychological predictors may prove useful in providing care to pediatric implant candidates. The results showed that preimplant IQ was not related to implant use or benefit; however, preimplant compliance and sociability significantly predicted use and benefit at 3 years after implantation. It appears that behavioral difficulties between mothers and children may limit the audiological benefit of pediatric recipients through compromised implant use. These findings suggest that interventions such as parent training and child behavior modification may prove useful in families when externalizing problems are manifested before implantation.

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QUALITY OF LIFE IN CHILDREN WITH COCHLEAR IMPLANTS

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INTRODUCTION

In the past 10 years, more than 8,000 children with profound hearing loss have been fitted with multichannel cochlear implants. Although speech perception and speech production abilities in many of these children have been studied extensively, few studies have documented quality-of-life changes in the pediatric population.¹⁻³ The early studies on quality of life reported parental observation of subjective changes following implantation with a 3M/House single-channel device.¹ To date, Kelsay and Tyler² are the only investigators who obtained subjective responses from a large group of parents of children with multichannel devices. These investigators used an open-

ended questionnaire that allowed parents to list the benefits and problems their child experienced as a result of cochlear implantation. However, open-ended questionnaires do not allow for quantification of the degree of benefit or the magnitude of problems reported.

In addition, though studies have reported parents' perception of subjective changes following implantation, to our knowledge, no studies have documented children's perception of benefit or problems associated with cochlear implant use. The purpose of this study was to quantify quality-of-life changes associated with use of a multichannel cochlear implant as determined by both pediatric implant recipients and their parents.

TABLE 1. COMPARISON OF MEAN BENEFIT RATINGS
MADE BY CHILDREN WHO COMPLETED
QUESTIONNAIRES AND THEIR PARENTS (N = 11)

Benefit	Parents	Children
Hear environmental sounds	4.55 (1)	4.40 (1)
Imitate or produce speech	4.30 (2)	3.64 (7)
Speech-reading and understanding	4.00 (3)	3.89 (4)
Child's attitude or behavior	3.64 (4)	4.00 (3)
Larger variety of activities	3.55 (5)	4.18 (2)
Make new friends	3.45 (6, 7)	3.72 (6)
Child's level of frustration	3.45 (6, 7)	3.55 (8)
Telephone use	3.18 (8)	3.73 (5)
Mean benefit rating	3.76	3.89

Scores for both parents and children ranged from 1 to 5 for most areas with few exceptions. Both groups gave "hear environmental sounds" at least rating of 2. Parents gave "speech production" rating of 3 or better, and children gave "attitude" rating of 2 or more. Ratings are based on 5-point scale, with higher scores indicating more benefit from using cochlear implant. Rank ordering of benefit is shown in parentheses.

METHODS

Subjects. All 38 families of the implanted children in our program were asked to participate in this study. A total of 21 families of pediatric implant recipients elected to participate. All children had received the Nucleus 22 channel cochlear implant system. Nineteen children used the spectral peak coding strategy; 1 child used the multi-peak strategy, and 1 child used the F0F1F2 strategy. Group A included 21 children, 10 girls and 11 boys, who were rated by their parents; their ages ranged from 3 to 20 years. The primary mode of communication was auditory-oral for 16 children, total communication for 4 children, and cued speech for 1 child. The children, on the average, had 4 years of experience with cochlear implant use (range, 0.6 to 9.9 years). Group B consisted of 11 children, a subset of the 21 described above, who also completed the survey. These children included 8 girls and 3 boys whose ages ranged from 6 to 20 with a mean age of 11 years. The mean length of implant use was 4.78 years (range, 0.6 to 9.9).

Procedures. Quality-of-life questionnaires were administered to the children and their parents. Most questions were derived from the parent responses reported by Kelsay and Tyler.² The questions were designed on a 5-point rating scale, such that higher scores indicated a more satisfactory quality of life, more benefit from cochlear implant use, or more problems associated with implant use. For example, a rating of 1 indicated "no benefit" or "no problem," whereas a rating of 5 indicated "great benefit" or "great problem."

The parent questionnaire consisted of 54 questions. In addition to a series of general questions about their children, the parents were asked to rate "How much benefit has your child received from a cochlear implant?" or "What problems has your child experienced as a result of cochlear implantation?" for each specific area addressed. All questionnaires were mailed to the parents and filled out in a paper-and-pencil format. No attempt was made to determine which parent actually filled out the questionnaire. Generally, the participants recorded both the mother's and father's names on the questionnaire form.

The children were given a modified version of the parent questionnaire that consisted of fewer test items and a simplified language structure. The older implant recipients (>12 years) filled out a 27-item questionnaire in a paper-and-pencil format. The younger implant recipients (≤12 years) were asked 18 questions as part of an interview with 2 examiners who had not worked with the children in the past. The children who used total communication were evaluated by an interviewer fluent in sign language. Questionnaire data were not obtained from very young children who could not be interviewed or from children who did not attend our data-gathering party. The child questionnaires, like the parent questionnaire, required the children to rate either the benefits or problems associated with implant use. In addition to using the rating scale, the implant recipients were asked 2 open-ended questions: "What do you like best about your cochlear implant?" and "What do you like least about your cochlear implant?"

RESULTS

Parent Responses. An analysis of the 21 parental ratings revealed that more than 80% of the parents reported at least some benefit in each of the 20 areas addressed, with the exception of telephone use (65%), indicating the wide range of positive quality-of-life changes associated with implant use. The mean benefit scores ranged from 2.65 to 4.71 (larger scores indicating greater benefit). Not surprisingly, the greatest benefits were noted for hearing environmental sounds (4.71), speech perception (4.62), and speech production (4.25). However, the child's sense of safety (4.05), self-esteem (4.05), vocabulary or language skills (4.00), and relationship with family (4.00) were rated as highly as overall communication skills (4.00). A mean benefit rating of 3.82 was calculated by averaging across all of the specific areas represented. This score indicates that overall, the parents believe that their children have received "quite a bit of benefit" from the use of a cochlear implant.

The mean problem scores ranged from 1.30 to 3.52 (larger scores indicating more problems). The highest problem rating (3.52) was given for the parents' concern about potential damage to the internal device. Other concerns were related to the equipment (2.52), limitations in participating in sports (2.35), and unrealistic expectations on the part of others (2.33). The lowest problem rating (1.30) was given for problems resulting from the surgical procedure. A mean problem rating of 2.13 was calculated by averaging across all 15 areas represented. This score indicates that overall, the parents believe that their children have experienced few problems from implant use.

Parent Versus Child Responses. Tables 1 and 2 show the mean benefit and problem ratings for the children and their parents. For better comparison, only the 11 implant recipients who completed the questionnaire and their corresponding parents are included in this analysis. The rank ordering of responses is shown in parentheses. Overall, Table 1 shows that the mean benefit ratings are remarkably similar for the two groups, indicating that both groups perceive that the implant has provided "a lot of help."

TABLE 2. COMPARISON OF MEAN RATINGS OF PROBLEMS BY CHILDREN WHO COMPLETED QUESTIONNAIRES AND THEIR PARENTS (N = 11)

Problem	Parents	Children
Need to take extra care when wearing device	2.36 (1)	2.64 (3)
Some loud sounds are bothersome	2.09 (2, 3)	3.16 (1)
Cumbersome equipment	2.09 (2, 3)	2.91 (2)
Acceptance by child's peers	2.00 (4)	2.20 (4)
Embarrassment about appearance of device	1.82 (5)	1.82 (5)
Child's resistance to wearing device	1.55 (6)	1.70 (6)
Mean problem rating	1.99	2.40

Ratings for both parents and children ranged from 1 to 5 for most areas. However, no parents gave "acceptance by child's peers" or "some loud sounds are bothersome" rating of 1. Ratings are based on 5-point scale, with higher scores indicating more problems associated with using cochlear implant. Rank ordering of problems is shown in parentheses.

Both parents and children gave hearing environmental sounds the highest benefit rating. The greatest discrepancy was noted for speech production. The parents rated this skill second in the list of 8, whereas the children rated it seventh. In addition, the children appeared to note the ability to participate in a larger variety of activities as a greater benefit than reported by parents. As indicated in Table 1, there was a wide range of ratings for each area, which suggests that for some children, receiving an implant did not change psychological state or lifestyle. However, all parents reported at least some benefit for their children in the areas of hearing environmental sounds and speech production. All of the children reported that the implant has helped them "feel happier."

The mean problem ratings shown in Table 2 indicate that overall, both groups report relatively few problems associated with implant use. The parents rated the "need to take extra care when wearing device" as the greatest problem associated with implant use, whereas the children gave "some loud sounds are bothersome" their highest problem score. The child's resistance to wearing the device was reported as the least of the problems by both the parent and child groups. The wide range of scores obtained for the individual areas suggests that although most of the children experienced few or no problems, some individuals experienced substantial problems as a result of cochlear implantation. An analysis of individual ratings can be used to assess concerns of parents or children who may require additional counseling or support.

When the children were asked "What do you like best about your cochlear implant?" most responses were related to hearing sounds. Comments such as "I can now hear" or "I hear much more" were given. This result is consistent with the highest benefit rating's being given

for hearing environmental sounds. In contrast, when asked "What do you like least about your cochlear implant?" 8 of 11 children gave responses related to the cumbersome equipment. Comments were "takes up too much space," "hard to wear with a dress," or "gets in the way of my body movement," whereas others said "nothing" or "don't know." No child reported that loud environmental sounds were the greatest concern, as might be expected from the rating noted in Table 2. Perhaps the children consider the equipment a constant source of trouble, whereas the loud sounds, though bothersome, occur less frequently.

DISCUSSION

Both the parents and children in this study reported substantial quality-of-life benefits and few problems after implantation of a multichannel device. In addition to providing information about the full range of benefits, questionnaire data allow clinicians to address both general concerns as a whole and specific concerns for each individual in order to minimize problems from implant use. Further research is needed to provide adequate data on the reliability of the specific questionnaires used in this study. Overall, the results support the value of quality-of-life questionnaires as a clinical tool in evaluating the perception of "real-world" benefit of a cochlear implant in the lives of children and their families.

Cunningham¹ found a difference in how parents and children viewed the advantages and disadvantages of the implant. However, his findings were based solely on the parents' comments that they were significantly more positive about the implant than they believed their children were. In the present study, the children and parents reported remarkably similar benefits from implant use, though children noted slightly more problems. The rank ordering of benefits and problems, though similar for parents and children, illustrated some important differences. Overall, the results support the value of obtaining information from the perspectives of both the children and their parents.

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SOCIAL INTERACTION OF PEDIATRIC COCHLEAR IMPLANT RECIPIENTS WITH AGE-MATCHED PEERS

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INTRODUCTION

Social competence is fundamental to the social adjustment of children and is often assessed directly with the Peer Group Entry Task (Peer Task).¹ The Peer Task requires a child to initiate interactions with 2 unfamiliar age- and gender-matched peers in a standardized setting. In general, Peer Task studies have shown that socially competent children are more successful in entering into an interaction with peers than are socially incompetent children.^{2,3} Hearing-impaired children have been shown to be less socially competent⁴ and to lack peer acceptance by hearing peers⁵ compared with normally hearing children. Knutson et al⁶ demonstrated that many pediatric cochlear implant candidates evidenced unsuccessful peer interaction in the Peer Task. Because the communicative limitations of hearing-impaired children can contribute to compromised social competence, it is expected that hearing-impaired children who receive audiological benefit from a cochlear implant would also evidence improved social competence with implant use. Therefore the present study was conducted to examine the effect of a cochlear implant on hearing-impaired children's social competence and to clarify the finding of a high rate of "failure to enter" (into play interactions) reported in the Knutson et al⁶ study.

METHODS

Subjects. The study included 2 samples: 1 hearing-impaired and 1 with normal hearing. The 34 hearing-impaired children (19 girls) had received multichannel cochlear implants at the University of Iowa. To be eligible for an implant, the subjects had to evince a profound (pure tone average of ≥ 95 dB hearing level) bilateral hearing loss before 18 months of age. Because the Peer Task requires children to be at least 6 years of age, the sample of implant recipients included those children who were old enough to participate, but the sample was unselected on variables other than age at testing. The ages at the time of the first Peer Task ranged from 6 to 14 years (mean, 8.0).

The sample of 20 normal-hearing subjects (9 girls) was recruited from the community. On the basis of the findings of Knutson et al,⁶ in which younger implant candidates failed to enter in the Peer Task, the comparison sample of hearing subjects was limited to children who were 6 or 7 years of age (mean, 6.4). Drawn from a pool of children who had previously participated in psychological research at the University of Iowa, the hearing sample was recruited by contacting parents by telephone and inviting their child to participate in a project investigating peer interactions. The recruitment process was designed to ensure that the children had no prior experience with the Peer Task or with each other.

Procedure. The implant candidates at the University of Iowa participated in a multidisciplinary evaluation over the course of several days. A psychological evaluation, of which the current study was part, was typically scheduled after children had met the audiological, medical, and radiologic criteria for implant eligibility. When the child was between 6 and 14 years of age at the preimplant as-

essment, the Peer Task was included at the preimplant psychological evaluation and at follow-up sessions. For subjects younger than 6 years at the time of preimplant assessment, the Peer Task was included at the first follow-up session after the child reached 6 years of age. For many, the first Peer Task occurred some time after implantation. After age 6, the Peer Task was scheduled at yearly follow-up sessions.

The Peer Task as used was virtually identical to that described by the developers.⁷⁻⁹ The subjects were tested with 2 age- and gender-matched children who had normal hearing. These "host" peers were recruited by the same procedure used for recruiting the hearing subjects, and they were paid \$10 for their participation. After informed consent from the parent and assent from the child were secured, the 2 "host" peers were introduced to each other and escorted to a laboratory room equipped with comfortable furniture and age-appropriate toys suitable for play by 3 children. The 2 hosts were allowed to interact alone in the laboratory for 5 minutes. After 5 minutes of free play, an experimenter introduced the entering subject to the 2 host peers. When the entering child was hearing-impaired, the introduction was accomplished with a combination of Signed English and oral statements. When the entering subject had normal hearing, only oral introductions were used. After the introductions, the children remained in the room to engage in free play for 20 minutes. The entire session was videotaped through a 1-way mirror for coding.

Coding of Videotapes. Each session was coded with a peer interaction code specifically developed to assess the entry and social interactions of hearing-impaired children in the Peer Task. The code included time-based measures of behaviors that are durationally meaningful,⁹ the recording of discrete behaviors that are not durationally meaningful, global ratings of interaction, and the occurrence of specific acts. The durational measures included the time elapsed before the subject commenced interaction with 1 or both hosts, the total time in interaction, and the duration of talking. The recorded discrete events included type of activity during non-entry (eg, passive observation, solitary activity), invitations initiated by the hosts, and instances of physical and verbal aggression. The categories of social interaction coded included watching the host peers, continuous interaction with 1 peer, and continuous interaction with both peers. The global ratings consisted of four 5-point Likert scales assessing the overall interaction in terms of friendliness-unfriendliness, acceptance-rejection, cooperation-uncooperation, and success of entry. The success of entry was the only rating that pertained exclusively to the entering subject.

Four coders were used, with each coding half of the sessions and each taped session being coded by 2 coders. Assignment of tapes to coders was done randomly to ensure that all coders were paired with each other, precluding the confounding of coder pairs with subjects and permitting an ongoing assessment of intercoder agreement. Seventeen sessions were randomly selected for coding by all coders to establish reliability among the coders. To

evaluate agreement between coder pairs, we used Cohen's κ statistic¹⁰ for categorical variables. For continuous variables, Pearson correlations and Cronbach's α were used. Variables were retained if the appropriate agreement coefficient was at least .70. The intercoder agreement (κ) of 3 categorical variables (behaviors observed without entry, aggression, and whether subject entered) reflected 100% agreement. The coding of invitations by the host peers directed at the entering subject was marginally reliable (73% agreement, $\kappa = .41$). The reliability of the coding of the continuous variables (durational and global ratings) assessed with the Pearson correlations ranged from .77 to .99, with a median of .91. Similarly, Cronbach's α values were at least .95 for each coded continuous variable. Thus the coding easily exceeded contemporary standards for scorer objectivity.

Parent Ratings. Two questionnaire measures were obtained from a parent of each entering child (generally the mother). These questionnaires were administered in routine assessments for the implant subjects and during the conduct of the Peer Task for the hearing subjects. The Child Behavior Checklist (CBCL),¹¹ a widely used measure of children's behavior problems, and the Missouri Children's Behavior Checklist (MCBC),¹² a true-false questionnaire, provided parent ratings of behavior on dimensions theoretically related to the Peer Task and social competence. From the MCBC, the Sociability scale was used; from the CBCL, the Social, Externalizing, Internalizing, and Total Problem scales were used, as was the report of involvement in social activities and extracurricular activities.

RESULTS

To determine whether cochlear implant use affected the behavior displayed during the Peer Task, we used 3 different analytic strategies. First, between-subjects analyses were completed to assess Peer Task behavior as a function of duration of implant use. Then, a subset of subjects who had repeated Peer Task tests were analyzed with the use of a repeated-measures ANOVA. Third, some Peer Task behavior was examined in single-case analyses. Finally, secondary analyses were conducted to understand entry failure.

Between-Subjects Analyses. For purposes of statistical analyses, the implant recipients were assigned to 2 groups. The short-term group ($n = 18$; 11 girls) consisted of those subjects who performed the Peer Task before 24 months of implant use. The long-term group ($n = 16$; 8 girls) comprised subjects whose Peer Task came after at least 24 months of implant use. At the time of testing, the ages of the short-term group ranged from 6 to 14 years (mean, 9.3) and the ages of the long-term group ranged from 6 to 14 years (mean, 8.6). Both groups of implant subjects were significantly older than the hearing comparison subjects ($F = 8.6, p < .001$).

Analysis of variance was used to compare the first Peer Task of the short-term group with the Peer Task of the long-term group and the single Peer Task of the hearing subjects. The peer group entry behaviors of these 3 groups

were similar on most variables, but 2 significant differences emerged. First, the long-term group had a significantly longer latency before entering the interaction. Second, and not surprisingly, the hearing group displayed more talking than did the 2 implant groups.

Within-Subject Analyses. Within-subject ANOVA of the coded behaviors was based on those implant recipients who participated in the Peer Task at preimplant, and again after approximately 1 year of implant use. These analyses did not detect any statistically significant differences from before implantation to the 1-year follow-up, suggesting little or no impact of the implant on the Peer Task.

Single-Case Analyses. Detailed behavioral analyses were completed on 5 subjects who had participated in the Peer Task before implantation and across several annual follow-up sessions. Three of these subjects displayed successful entry and effective peer interaction at the preimplant session, and this level of entry success was maintained at each follow-up session. As a result of the successful entry before implantation, there was no room for improvement after implantation. The fourth subject's interaction with peers before implantation and at the 8-month follow-up was much less successful than that of the 3 successful children. Although the fourth subject entered the room without reticence, he spent most of the session failing to interact with either peer. At the 12-month follow-up, he entered but interacted with only 1 peer, and for less than half the session. The fifth subject actually evidenced a decline in social competence over time. Before implantation, this subject had a successful entry that was comparable to that of other successful children. At the 12-month follow-up, however, the entry was rated as unsuccessful, with a latency of more than 6 minutes. Only minimal interaction with either host occurred, and no collective interaction was coded.

Implant and Hearing Subjects. To complete an age-matched analysis, we compared implant recipients who were either 6 or 7 years old at their first Peer Task to the group of hearing subjects with respect to coded behaviors and entry success. There were 14 such subjects (7 girls). Several important differences emerged between the 2 groups. First, the implant subjects took longer to enter ($t = 2.8, p < .01$) and had less continuous interaction ($t = -2.1, p < .05$) with peers than did the hearing subjects. In addition, the interaction of the hearing subjects was characterized as more verbal ($t = 4.0, p < .001$), more friendly ($t = 3.1, p < .01$), more accepting ($t = 3.3, p < .005$), more cooperative ($t = 2.9, p < .01$), and more successful in entry ($t = 2.8, p < .01$) than that of the implant subjects. Therefore, when matched in age and task experience, the hearing-impaired children who received cochlear implants did much more poorly on the Peer Task than did the children with normal hearing.

Entry Failure. Eight implant subjects did not interact with the 2 peers during at least 1 session. One hearing subject did not interact. Therefore, whereas 27.6% of implant subjects failed to enter on at least 1 occasion, only 5% of the hearing subjects failed to enter. The pattern of unsuccessful entry differed among the 8 subjects. Inter-

estingly, 1 failed to enter after having had successful entry 12 months earlier. Two subjects entered after failing at earlier sessions. Only 1 subject failed to enter across repeated annual tests. When those who always entered successfully were contrasted with those who evinced entry failure, only 1 statistically significant difference emerged. The non-entering implant subjects were approximately 2 years younger than the entering implant recipients at their first session ($t = 2.53$, $p < .02$). When the behavior displayed during non-entry was examined, solitary play and passive observation emerged as the predominant attributes of the non-entering children. Of the subjects who did not enter, 78% engaged in some solitary activity, and 22% engaged in solitary activity exclusively. Sixty-seven percent of the non-entering children engaged in passive observation of the hosts, and 22% engaged in passive observation exclusively.

Because the success of entry could reflect how hospitably the host children behave toward the entering child, the tapes of the hearing children and the younger sample of hearing-impaired children were re-coded by a new team of coders to assess the behavior of the host children. After the reliability of the new coders was established, the behaviors of the host children were compared as a function of the hearing status of the entering child. Although the amount of interaction between the hosts was reduced after the introduction of the third child, no significant differences in coded behavior were detected as a function of the hearing status of the entering child. Most important, the host peers made invitations to the entering child at rates that did not differ between the 2 groups ($\chi^2[1] = 2.85$; not significant). The coded behavior of the host children was then contrasted between sessions in which there was no entry and sessions in which there was successful entry. Again, there was no difference between groups. In 56% of the cases of non-entry, there was less than 2.5 minutes of host interaction, but in 44% of the cases of non-entry, there was more than 7.5 minutes of interaction between the hosts.

Parental Ratings. The CBCL and the MCBC scores from the first session of the children who failed to enter were compared with the CBCL and MCBC scores of the subjects who never failed to enter. On all of the behavior problem scales and social competency scales, the parents of both successful and unsuccessful enterers described their children similarly. Moreover, the mean scores of both the entering and the non-entering subjects were within the normal range.

DISCUSSION

The findings of this study did not support the hypothesis that social competence, as measured by the Peer Task, would be improved with use of a cochlear implant. The present study showed that there were no differences in the peer group entry behavior of subjects with less than 24 months of implant use and that of subjects with 24 or more months of implant use. Similarly, the results of the within-subject analysis showed no obvious improvement in peer group entry behavior over time as a result of the cochlear implant. Although these findings are disappoint-

ing, it is important to note that audiological benefit from an implant is achieved slowly and typically requires more experience than was achieved by the subjects in the present study. Additionally, although some subjects evinced poor social competence in the Peer Task, most subjects had competent interactions in their first Peer Task. Therefore dramatically improved performance might not be detectable among older children in the study.

According to the literature, some hearing-impaired children are likely to exhibit behaviors associated with a lack of social competence,^{3,13} which include having difficulty interacting with peers. This study established that younger hearing-impaired children had more difficulty with peer group entry than did age-matched normal-hearing children. This finding is consistent with other work in which young hearing-impaired preschoolers spent less time interacting and more time in solitary play than older hearing-impaired preschoolers.¹⁴ Because lack of entry in the Peer Task has only been reported in a single study of normal-hearing children,¹⁵ the findings in the present study and earlier work⁵ indicate that a lack of entry may be critical in considering the social opportunities for younger children with cochlear implants. Because there were no identifiable patterns of host behavior that predicted unsuccessful entry, it is probable that the hearing-impaired children failed to respond to the invitations and social overtures of the hosts. Future research should consider whether unsuccessful entry can be avoided by giving young hearing-impaired children guidance as to how to recognize and respond to invitations from others. The failure of standardized parent ratings to correlate with coded behavior underscores the limitations of parent ratings of children's behavior¹⁶ and documents the need for direct assessment of implanted children rather than relying on parental reports.

CONCLUSIONS

An important implication of this study is the possibility of identifying children who have difficulty in peer group entry and intervening to enhance their peer interactions. Because use of the implant in an oral environment may facilitate implant benefit, helping young implant recipients by improving their social skills might pay dividends in greater implant use and benefit as well as enhance the social competence of the children.

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PSYCHOLOGICAL CONSEQUENCES OF PEDIATRIC COCHLEAR IMPLANT USE

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INTRODUCTION

Studies conducted over the last decade have demonstrated that although substantial outcome variability exists, cochlear implants can provide children and adults with significant benefits to speech perception and speech production measures.¹⁻⁶ Additionally, recent work⁷ demonstrates that cochlear implant use by postlingually deafened adults results in sustained improvements in several areas of psychological functioning. Greater controversy exists over the potential psychological sequelae of implantation in prelingually deafened children. Some researchers have suggested that cochlear implant use reduces the academic, social, and emotional difficulties commonly reported in deaf children.⁸ In contrast, some deaf activists have suggested that cochlear implant use threatens the psychological well-being of prelingually deafened children.⁹ Because of the lack of published research in this area, these countering claims have remained largely conjectural. However, given the significant, albeit imperfect, relationship between psychological difficulties and degree of hearing loss in hearing-impaired children without implants,¹⁰ as well as the positive but imperfect correlation between audiological benefit and positive psychological outcomes in postlingually deafened adult cochlear implant users,⁷ it is reasonable to hypothesize that audiological benefit could afford pediatric implant recipients some psychological benefit.

The current study was designed to assess the presence and direction of psychological changes after pediatric cochlear implantation and to determine the relationship between audiological benefit and psychological change.

METHODS

Subjects. The subjects were drawn from an ongoing

study of prelingually deafened children who received Nucleus multichannel cochlear implants at the University of Iowa. Before implantation, children were required to have bilateral profound deafness (pure tone average of ≥ 95 dB hearing level) and to fail to benefit from hearing aids. The analyses reported below were conducted on a subset of 24 children from the ongoing study (13 boys and 11 girls) for whom annual follow-up data were available through 36 months after implantation. Their mean age at implantation was 5.6 years (range, 2 to 13). Most attended mainstream schools in their communities, usually with the aid of sign language interpreters.

Procedure. The children and their parents took part in a multidiscipline assessment at the University of Iowa before implantation and at annual follow-ups. The psychological evaluation included multiple assessment procedures not analyzed in the current study, including diagnostic interviews and videotaped observations. All psychological evaluations were conducted by graduate students in clinical psychology who had experience in child assessment and who were familiar with manual communication techniques. A sign language interpreter was used to facilitate the evaluation of children who were at least 6 years old.

Psychological Measures. The subjects were given 3 general tests of intelligence. The Hiskey-Nebraska Test of Learning Aptitude¹¹ was specifically designed to measure the intelligence of children with hearing impairments. The Leiter International Performance Scale¹² is a commonly used nonverbal measure of intelligence. These tests require no verbal instructions or responses and were typically administered before implantation. Children who were at least 6 years old completed the Wechsler Intelligence Scale for Children (WISC-III)¹³ at the preimplant appoint-

TABLE 1. CORRELATIONS BETWEEN MEAN FOLLOW-UP MATERNAL CBCL SCORES AND AUDIOLOGICAL SCORES AT 36-MONTH FOLLOW-UP

	Externalizing	Internalizing	Total Problems
Consonants	-.55*	-.47	-.66†
MTS-Words	-.65†	-.50	-.75†
MTS-Stress	-.63†	-.54*	-.71†
PBK-Phonemes	-.71†	-.49	-.69†
PBK-Words	-.60*	-.44	-.58*
Vowel Features	-.75†	-.58*	-.83†
WIPI	-.58*	-.40	-.60*

*p < .05.
†p < .01.

ment and at each follow-up with the assistance of a sign language interpreter. At each evaluation, the parents completed questionnaires regarding the child's behavior and home environment. Among these was the Child Behavior Checklist (CBCL),¹⁴ a reliable and valid standardized rating scale designed to assess child behavior problems. Three composite behavior problem scores can be obtained from the CBCL: Internalizing, Externalizing, and Total Problems.

Audiological Measures. At the preimplant and follow-up evaluations, standardized speech perception tests were administered by audiologists. The test battery included the Monosyllabic-Trochee-Spondee test (MTS), the Word Intelligibility by Picture Identification test (WIPI), the Phonetically Balanced-Kindergarten Word Lists (PBK), the low-verbal monosyllabic and spondee Early Speech Perception tests, and a 4-choice vowel recognition measure (Vowel Features).¹⁵

RESULTS

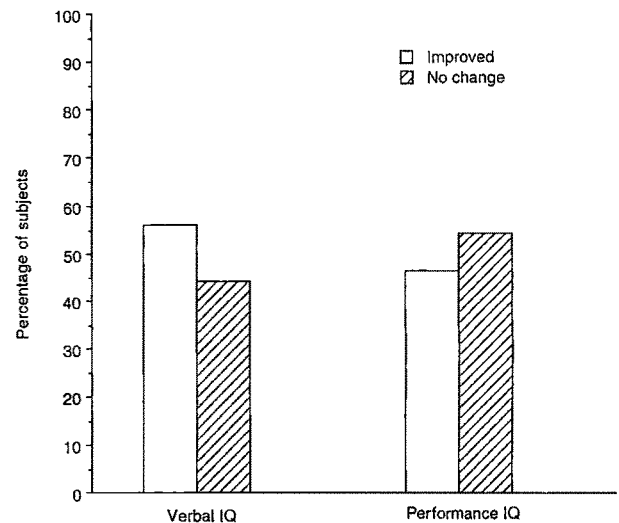
Relationships Between Psychological and Audiological Measures. The scores for the WISC-III and the CBCL were averaged across the follow-up period to produce mean follow-up scores for Verbal, Performance, and Full Scale IQ on the WISC-III and for Externalizing, Internalizing, and Total Problems scores on the CBCL. Correlations were then computed between each of these psychological measures and the battery of speech perception tests. Some children did not complete all 5 audiological tests at each interval; as a result, some analyses were conducted with as many as 3 missing subjects.

Table 1 shows the correlations between the mean fol-

TABLE 2. CORRELATIONS BETWEEN MEAN FOLLOW-UP WISC-III VERBAL IQ AND AUDIOLOGICAL SCORES AT FOLLOW-UP

	12 mo	24 mo	36 mo
Consonants	.60†	.61†	.45*
MTS-Words	.54†	.58†	.46*
MTS-Stress	.59†	.68†	.46*
PBK-Phonemes	.28	.52†	.26
PBK-Words	.14	.39	.24
Vowel Features	.59†	.53†	.39
WIPI	.22	.69†	.39

*p < .05.
†p < .01.



Percentage of subjects evidencing 0.5 SD or greater change in WISC-III intelligence test scores.

low-up maternal CBCL and audiological test scores. There were strong significant negative correlations between the mean follow-up Externalizing and Total Problems scores and the speech perception scores at the 36-month follow-up. The correlations between Internalizing problems and speech perception were also negative but more modest in size; most of those comparisons did not reach significance at the $p < .05$ level.

Table 2 shows the correlations between the mean follow-up Verbal IQ scores on the WISC-III and the audiological scores at the 12-, 24-, and 36-month follow-ups. The correlations between the mean follow-up WISC-III Performance IQ and audiological scores generally did not reach significance at the $p < .05$ level.

Psychological Change After Implantation. The subjects were classified according to whether their WISC-III Verbal or Performance IQ scores evidenced a 0.5 SD or greater change across the follow-up period. The WISC-III population norms indicate an SD of 15 points; therefore subjects who gained at least 8 IQ points were classified as "improved," and subjects who lost at least 8 IQ points were classified as "deteriorated." Subjects for whom any change in IQ was less than 8 points were classified as "unchanged." As the Figure shows, 56% of the children evidenced a 0.5 SD or greater increase in Verbal IQ, and 46% evidenced a 0.5 SD or greater increase in Performance IQ. No children evidenced deterioration in IQ across the follow-up period.

DISCUSSION

Although before implantation the children in this study exhibited some cognitive and emotional deficits in comparison with norms for hearing children, for the most part, they fell within what is considered the "normal range" on most measures of psychological functioning. For this reason, the results of this study are most usefully framed within the context of varying levels of adaptive functioning rather than in terms of pathology.

Maternal reports of Externalizing behavior (such as ag-

gression, destructive behavior, and attention problems) and Total behavior problems were negatively correlated with a wide range of speech perception measures at 36 months. One possible conclusion would be that behavior deteriorates over time for children who receive little audiological benefit from their implants. However, given that preimplant Externalizing behavior problems predict lesser audiological benefit at follow-up (Knutson et al, this supplement, pp 100-103), a more credible interpretation is that children's behavior problems may limit the audiological benefit they ultimately receive from their implants. For example, behavior problems may make it difficult for parents to enlist their children's compliance with implant use and speech training.

Most of the children had gained at least 0.5 SD in WISC-III Verbal IQ at follow-up. Because the WISC-III was always administered with the aid of an interpreter, the children's improvement appears to represent a genuine increase in verbal abilities rather than simply an increased facility with spoken English. Moreover, the mean Verbal IQ at follow-up was correlated with a wide range of speech perception measures. Preimplant IQ did not predict audiological benefit in this sample (Knutson et al, this supplement, pp 100-103) or in other studies involving postlingually deafened adults.¹⁶ Thus, we conclude that higher-IQ children do not receive greater audiological benefit from implantation; rather, children with greater audiological benefit exhibit higher Verbal IQ scores at follow-up.

CONCLUSION

Despite the predictions of deaf activists, no evidence of negative psychological sequelae of cochlear implantation was found. The present study suggests that the audiological benefits of pediatric cochlear implantation may lead to substantially improved cognitive abilities and that implants produce no ill effects on psychological well-being. The data are also consistent with the hypothesis that children who present with externalizing behavior problems may realize less benefit from a cochlear implant.

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PARENTAL PERCEPTIONS OF THE IMPACT UPON THE FAMILY OF COCHLEAR IMPLANTATION IN CHILDREN

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INTRODUCTION

The past 10 years have shown cochlear implantation to be an effective method of providing profoundly deaf children, who cannot benefit from conventional hearing aids, with auditory stimulation. There is much research on the effectiveness of the cochlear implant in children. Most researchers emphasize the importance of family members in the process of rehabilitation for children with cochlear

implants. A general aim of the intervention is to improve the quality of life, a multidimensional concept that involves physical aspects, psychological adjustment, and social well-being. Although much research has been directed at physical aspects of performance with a cochlear implant, the psychological and social consequences are less well understood.

A profoundly deaf child who receives a cochlear im-

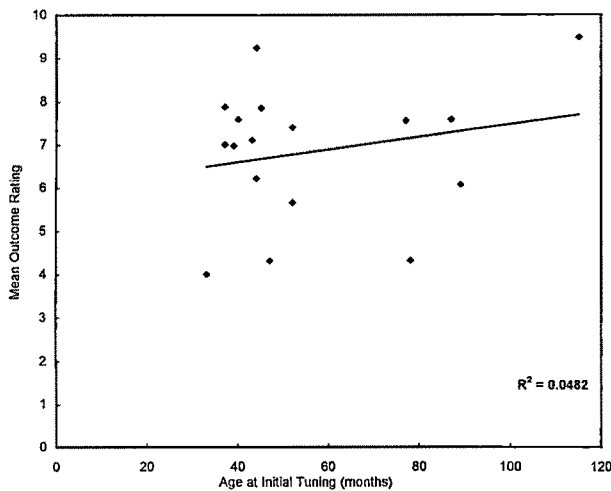


Fig 1. Mean outcome rating and age at initial tuning for 17 children. Note cluster of 8 children who were under 48 months of age at initial tuning who had high outcome ratings.

plant is affected in not only his or her own quality of life but also in that of the whole family. It seems probable that cochlear implantation that leads to improved communication in a family could be seen as an enhancer of quality of life for both the child and the family as a whole. It is possible, however, that the stress of the implantation and rehabilitation process could diminish the quality of life for all.¹ It would be hoped that as these stressors are reduced over time, positive results would become apparent and increase the quality of life in the family.

The literature raises specific research questions that suggested the following hypotheses: 1) in terms of expectations, quality-of-life ratings would be higher when outcomes were as good as or better than predicted; 2) in terms of stress factors, quality-of-life ratings would be lower when stress factors were perceived as great; 3) in terms of social support, quality-of-life ratings would be higher when levels of social support were perceived as high; and 4) in terms of outcomes, quality-of-life ratings would be higher when outcomes were perceived as good.

The major aim of this study was to increase knowledge about the stressors affecting the families of children with cochlear implants and about factors that help families to cope. The study aimed to examine the perceptions of parents of children with cochlear implants by exploring the parents' feelings about the process of implantation, its outcomes, and the support the families received. The children were not asked for their perceptions; these were reported by the parents. The study also aimed to investigate the relationship between these perceptions and the quality of life as reported by the parents.

METHODS

A rating scale was developed that would allow exploration of the perceptions of the parents of children who had received cochlear implants. There were 74 statements to rate in 4 sections: 1) parental expectations before implantation; 2) parental view of the realization of expectations, including parental perceptions of other outcomes

of cochlear implantation and parental responses to stress factors associated with hearing-impaired and cochlear-implanted children;² 3) parental view of amount of social support; and 4) items relating to measures of quality of life. Questionnaires were sent to 22 sets of parents whose children had received cochlear implants a minimum of 6 months before April 1997. Seventeen of the questionnaires were returned completed. Note was taken of the age of the children at initial tuning and, for the purposes of this study, the length of time since the children had undergone implantation.

RESULTS

Parental Expectations. A set of 20 items asked respondents to think back to how they felt before their children underwent implantation and to report, retrospectively, their expectations for their child in terms of communication, behavior, speech, and education, for example, "I expected my child's behaviour would improve as a result of the cochlear implant." Parents were asked about their current situation and expectations about the same subjects, for example, "My child's behaviour has improved since implantation." For 9 respondents, an expectations questionnaire had been completed before implantation, and this was correlated with their retrospective views.

The validity of the retrospective measure of parental expectations was shown to be weak, with only 7 statements showing a positive correlation with preimplant expectation responses. However, the results did indicate that the parental expectations were not inappropriately increased. The preimplant expectations tended to be lower for children who were relatively young or old at the time of implantation.

Perception of Outcome. The second part of the questionnaire investigated the current situation and included 46 questions relating to stress factors and to other outcomes, for example, "Since implantation, my child can communicate better." Parents indicated their responses, and these were transposed onto a linear scale (SA = strongly agree, A = agree, D = disagree, SD = strongly disagree, with SA = 10 [high score] and SD = 1 [low score]). The answers showed higher ratings being given for finding schoolwork easier and for progress in reading.

The scattergram in Fig 1 shows a cluster of 8 children who were younger than 48 months of age at initial tuning with high outcome ratings. No direct relationship was shown between mean outcome rating and age at initial tuning. The 8 younger children were perceived as doing well by the parents. A study by Cohen and Waltzman,³ found performance to be enhanced when implantation was performed between the ages of 2 and 3 years; it is suggested that this is because these children can take advantage of the critical learning years. Tyler et al⁴ reported that children with some experience of language tend to perform better with cochlear implants than do the congenitally deaf. Five of the 6 implant recipients studied by Geers and Moog⁵ received their implants after the age of 3, but while still in the critical learning years. Geers and Moog found that young cochlear implant users acquired

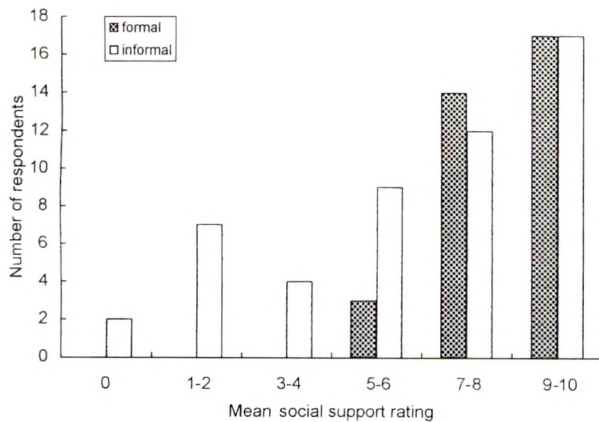


Fig 2. Mean social support rating from informal and formal sources, as reported by parents.

expressive vocabulary at a rate equivalent to or faster than that of normal-hearing children. These cases suggest that children with implants who have missed the usual language-learning years can still acquire language quickly.

Stress Factors. The participants responded to 15 statements relating to stress factors, for example, "I feel anxious that the cochlear implant device will malfunction." The parents' responses were transposed onto the linear scale ($SA = 10$, $SD = 1$). The mean stress score across the subjects was 3.63, suggesting that no one was experiencing extremely high stress associated with hearing impairment or cochlear implantation. The mean stress scores were correlated with a mean outcome score and a quality-of-life score, and although the correlation coefficients were not significant, they were negative, suggesting that lower levels of stress are associated with a higher quality of life. Of the 14 participants to whom the item "The child's brother(s)/sister(s) seem jealous of all the extra attention he/she gets" was applicable, 8 responses demonstrated agreement. This provides some evidence that the siblings of children with cochlear implants have some difficulty coping.

Parental Reports of Amounts of Social Support. Part Three of the questionnaire asked the respondents to rate the social support received from 5 different sources on a 10-point scale, 1 indicating no support and 10 indicating much support. Ratings referring to support from 5 sources were collected. The sources were divided into 2 categories: 1) "informal" social support from grandparents, friends and neighbors, and other relatives and 2) "formal" social support from education and the cochlear implant team. A bar graph from the 2 categories is shown in Fig 2. The mean social support rating from formal sources is 8.4, and the mean from informal sources is 6.4. The difference between the means is highly significant ($p < .001$).

Measure of Quality of Life for Children With Implants, Their Parents, and Their Families. The respondents were given 3 items relating to their current quality of life. The ratings were on a scale of 1 to 10, with higher numbers signifying better quality of life. The 3 statements about quality of life were designed to reflect the perceptions of the parents at the time they completed the questionnaire.

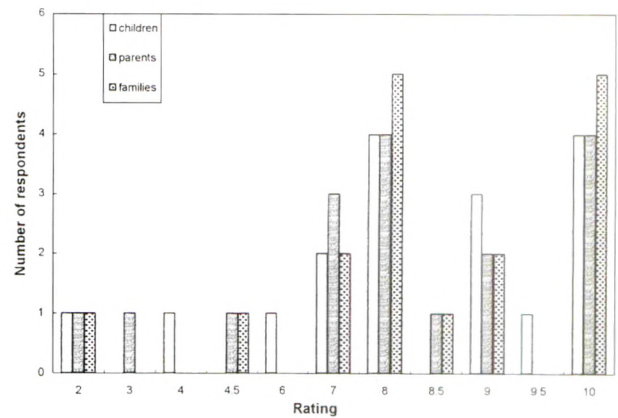


Fig 3. Quality of life after implantation, as rated by parents for families, children, and selves.

It was expected that their thinking would have been focused by the previous sections of the questionnaire. The parents were asked to think about issues such as independence, communication, happiness, and satisfaction for the life of the implant-recipient child, their own lives, and the life of the family as a whole. The mean ratings for quality of life were 7.9 for the implant recipients, 7.8 for the parents, and 7.1 for the family as a whole. The bar graph in Fig 3 illustrates a quality-of-life rating of greater than 7 for 14 of the 17 implant recipients and their parents and for 15 of the 17 whole families. A high positive correlation was shown between the quality-of-life and mean outcome scores ($r = .77$; $p < .001$). The social support and mean outcome scores showed a borderline correlation ($r = .55$; $p < .05$).

DISCUSSION

Expectations. The hypothesis predicting a higher quality-of-life measure when outcomes were as good as or better than predicted was not supported in this study. However, the scores of preimplant expectations ranged from 2.4 to 3.4, suggesting that parental expectations were not inappropriately increased. Further study needs to be conducted on preimplant parental expectations to ensure that the parents have received relevant information and have had every opportunity to discuss their expectations. Lloyd⁶ reports that many parents feel that gathering as much information as possible from as many people as possible is essential. The process of assessing a child's suitability for cochlear implantation includes assessment of the family's expectations. Counseling is provided as necessary to increase the parents' understanding of possible outcomes.

Outcomes and Quality of Life. The parents indicated that their perceptions of improved quality of life were associated with positive outcomes.

Stress Factors. No significant correlation was shown between stress ratings and quality-of-life ratings in this study.

Social Support. A positive correlation was shown between quality of life and social support ($p < .05$), suggesting that the quality of life is higher when levels of

social support are perceived as high, particularly support from formal sources.

Implications for Practice. The results of this study suggested the following: 1) the cochlear implant team and school staff were viewed as supportive, giving advice and practical help, and this outcome suggests the importance of these agencies; 2) a high level of perceived social support was associated with lower stress ratings and better outcomes, and hence this may be a very important factor to consider before implantation; 3) parental expectations need to be realistic; and 4) consideration must be given to support for siblings to help them feel important and of value to the cochlear implant wearer.

CONCLUSIONS

As an increasing number of children receive cochlear implants, it is important to find out not only how successful cochlear implantation is in providing profoundly deaf children with sound perception, but also how the process of cochlear implantation and the long training period that follows it affect the lives of child implant recipients and their families.

This study investigated the perceptions of parents of child recipients of cochlear implants with regard to their initial expectations, their feelings about the process, actual outcomes, and the amount of social and formal support received. Parental evaluations of current quality of life were also examined in relation to these perceptions.

Overall, the parents who participated in the study seemed pleased with their implant-recipient children's progress.

Some children with implants learn to communicate orally with great proficiency; those who achieve less success in learning to talk still benefit from the ability to perceive environmental sounds, which they would lack without the device. The process of assessment, hospitalization, tuning sessions, and ongoing rehabilitation and training means hard work and stress for the families of children with cochlear implants. This study has indicated that social support may decrease stress and ameliorate the quality of life in such families. Further research is necessary to discover more about what can be done to assist children with cochlear implants, their siblings, and their extended families.

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STRUCTURE OF MENTAL LEXICONS OF CHILDREN WHO USE COCHLEAR IMPLANTS: PRELIMINARY FINDINGS

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INTRODUCTION

Logan¹ has proposed that children older than 2 years with normal hearing organize and retrieve words from their mental lexicons using a phoneme-based strategy similar to that of adults. It is not clear whether the mental lexicons of children with profound deafness who use cochlear implants (CIs) are similarly organized, but the structures of such lexicons may indicate how these children acquire the ability to recognize and produce spoken words. To examine this, errors produced by such children on the Lexical Neighborhood Test (LNT),² an open-set, monosyllabic word recognition test, were analyzed within the framework of the Neighborhood Activation Model (NAM).^{3,4} This model proposes that spoken word recognition occurs in the context of phonologically similar words, such that recognition of a spoken word is dependent on 1) the frequency of occurrence of the word and 2) words in the

lexicon that are phonologically similar (by single-phoneme substitution, addition, or deletion) to the target word ("neighbors"), including both the number of neighbors ("neighborhood density") and the neighbors' mean frequency of occurrence in the language ("neighborhood frequency").

METHODS

Participants. Fifteen children with prelingual (<3 years) profound hearing loss who received the Nucleus 22 cochlear implant (5 implementing a multipeak [MPEAK] strategy and 10 a spectral peak [SPEAK] strategy) participated. The mean age at onset of profound loss was 0.2 ± 0.5 years, the mean age at implantation was 5.2 ± 1.9 years, and the mean age at time of testing was 7.3 ± 1.9 years. Seven used oral communication (OC), and 8 used simultaneous communication (SC). Children were se-

TABLE 1. PERCENT WITHIN-NEIGHBORHOOD RESPONSES (ADULT LEXICON)

	Oral Communication		Simultaneous Communication	
	Easy	Hard	Easy	Hard
Correct	63.7%	52.1%	36.5%	23.5%
Incorrect but neighbor of target	8.0%	18.4%	11.6%	22.0%
Total (target or neighbor of target)	71.7%	70.5%	48.1%	45.0%

lected on the basis of their ability to complete the LNT.

Materials and Testing Protocol. At the 2-year postimplant interval, each child was administered the LNT. This open-set test was chosen over a closed-set one because the multiple-choice format of the latter provides only minimal information about the structure of the lexicon and its contribution to word recognition. The LNT includes target words that are "easy" and words that are "hard" to recognize. "Easy" words occur frequently in the language and reside in neighborhoods that are sparse and of low mean frequency. "Hard" words are of low frequency and reside in dense neighborhoods with high mean frequencies. The test was administered by live-voice presentation without visual cues at approximately 70 dB sound pressure level. Participants were instructed to repeat the words they heard; to avoid confounds with pure production errors, participants were also asked to sign, spell, or write their responses or to demonstrate comprehension of the meanings of their responses.

Analysis. The responses were scored on the basis of percentages of phonemes and words correct and then analyzed according to parameters proposed in the NAM (see above). Two computerized lexical databases represented the mental lexicon: 1) to represent an adult lexicon, a 20,000-word on-line pocket lexicon,⁵ and 2) to represent a child lexicon, a 600-word lexicon for 5-year-old children.⁶ Separate calculations were performed for users of OC and SC, and for easy and hard words.

RESULTS

Percent Correct Words and Phonemes. For OC users, the percentage of words correct was 63.7% for easy and 52.1% for hard words. For SC users, the scores were 36.5% for easy and 23.5% for hard words. For OC users, the percentage of correct phonemes was 77.1% for easy and 71.6% for hard words. For SC users, the percentage of correct phonemes was 58.1% for easy and 46.8% for hard words.

Within-Neighborhood Responses. With the use of the

TABLE 2. PERCENT RESPONSES "HARDER" THAN TARGETS (ADULT LEXICON)

	Oral Communication		Simultaneous Communication	
	Easy	Hard	Easy	Hard
Lower in frequency of occurrence than targets	76.9%	53.7%	66.9%	60.3%
From denser neighborhoods	78.6%	56.1%	61.6%	38.1%
From neighborhoods with higher frequencies	64.3%	48.8%	61.6%	44.9%

TABLE 3. PERCENT RESPONSES "HARDER" THAN TARGETS (CHILD LEXICON)

	Oral Communication		Simultaneous Communication	
	Easy	Hard	Easy	Hard
Lower in frequency of occurrence than targets	69.0%	44.9%	58.3%	49.5%
From denser neighborhoods	72.8%	44.4%	68.9%	42.0%
From neighborhoods with higher frequencies	65.2%	46.0%	63.6%	42.7%

adult lexicon, it was determined whether responses resided in the neighborhoods of the relevant target words. Table 1 shows the percent responses residing in the target's neighborhood, also broken down by correct (target) and incorrect (but in the neighborhood of the target) responses.

Frequency and Neighborhood Structures of Responses (Adult Lexicon). The frequency of occurrence and neighborhood characteristics (neighborhood density and frequency) were determined for all responses. Separate calculations were performed with the adult lexicon⁵ and the child lexicon.⁶ The frequencies and neighborhood characteristics of target words and responses were then compared to determine whether responses were "easier" or "harder" than targets. Table 2 shows the percentage of responses with characteristics of being "harder" than the target (lower frequency, from denser neighborhoods with higher mean frequencies).

Frequency and Neighborhood Structures of Responses (Child Lexicon). Using the word list for 5-year-olds,⁶ we determined the frequency and neighborhood characteristics of responses to both easy and hard words. Table 3 shows the percentage of responses that were "harder" than the target (lower frequency, from denser neighborhoods with higher mean frequencies).

DISCUSSION

As expected, *phonemes correct* scores were higher than *words correct* scores for both easy and hard words and for both OC and SC users. The mean length of words on the LNT is 3 phonemes — evidence that children receive at least partial information regarding phonemes in words through the CI. Also as expected, both phonemes- and words-correct scores were higher for users of OC than for users of SC; this may indicate greater attention to acoustic information for the OC users than for the SC users. Further evidence that CIs transmit information regarding the phoneme structure of words lies in the fact that between 45.0% and 71.7% (depending on communication mode and the easy-versus-hard distinction) of responses were in the neighborhood of the target. For users of OC especially, this indicates a structure of the lexicon much like that of adults, that is, a phoneme-based strategy of organization and extraction of words.

When analyzed within the adult lexicon, and depending on the neighborhood structure of targets and the communication mode, between 53.7% and 76.9% of responses were lower in frequency than targets, between 38.1% and 78.6% of responses came from neighborhoods more dense

than those of targets, and between 44.9% and 64.3% of responses came from neighborhoods with higher mean frequencies than those of targets. We therefore concluded that a large number of responses were "harder" than their targets when assessed within the adult lexicon. Similar results were found when responses were analyzed within a children's lexicon. Although "harder" responses may be counterintuitive, the open-set response format of the LNT makes it effectively both a perception and a production task, and little research has been conducted on frequency and neighborhood effects in production tasks.

A related question addresses the proper context in which to analyze the frequency and neighborhood structure of responses on the LNT. Frequency and neighborhood structure have traditionally been assessed in the context of adult vocabularies.³ As has been shown elsewhere,⁷ however, the large differences between children's and adults' lexicons give rise to similarly large differences in the neighborhood structures of words in those lexicons. Test items for the LNT were selected from analyses of the vocabularies of 1- to 5-year-olds,¹ somewhat younger than the children in the present study. The present study analyzed children's lexicons in the context of a spoken word list⁶ investigated in previous studies of children's lexicons⁷; moreover, this list was likely more appropriate than Logan's¹ for the age of the children under study here, given delays in language development. However, of the 100 items on the LNT, 45 do not appear in the child lexicon used, so that almost half of the target items had to be assigned zero frequencies when analyzed within the children's lexicon. A similar strategy was necessary for many

of the responses. Further questions arise regarding elicitation procedures (eg, spontaneous¹ versus elicited⁶) and the status of grammatically inflected forms.

Therefore, although neighborhood structure analyses of children's responses may have more face validity in the context of a putative children's lexicon, it is also true that determining the appropriate children's lexicon is a matter of debate. For longitudinal studies, adult lexicons may still be the best context for neighborhood structure analyses.

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PEDIATRIC AUDIOLOGISTS' VIEWS ON COCHLEAR IMPLANTATION

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INTRODUCTION

The average age of cochlear implantation continues to decline as the manufacturers seek to obtain US Food and Drug Administration approval in children as young as 18 months of age and off-label implantation in younger children becomes more common. The acceptance of implantation in children at an earlier age will depend in large part on the attitudes and beliefs of pediatric audiologists. Not only must there be an acceptance of early implantation, but the option must be aggressively pursued. This may be accomplished in part by discussing implantation with the family early in the process of diagnosis and management to prepare them for the possibility. Pediatric audiologists were surveyed to obtain information about their current practices and views on cochlear implants.

METHODS

Surveys were mailed to 222 audiologists who described their primary employment setting as a children's hospital. The surveys assessed training, experience, attitudes,

and practice (see Table). The mailing list used was obtained through the American Speech-Language-Hearing Association.

RESULTS

A response rate of 65% was achieved. The responses indicated that 92% of the respondents have recommended that families consider the option of cochlear implantation (see Table, item 1). In addition, 83% feel comfortable discussing this subject with families they serve (item 6). Cochlear implant team members were more likely to feel comfortable than others (100% versus 76%; $p = .003$). No other effects of team membership, education, or being at an implant site were found, with a criterion of $p < .01$ used to compensate for multiple comparisons.

At the time of the survey, no implants were labeled for routine use below 2 years of age, and off-label implantation may not have been prevalent. Still, 68% indicated that they would consider referring a child by 18 months, if age were not a criterion in referring a patient (item 4).

PEDIATRIC AUDIOLOGISTS' VIEWS ON COCHLEAR IMPLANTATION (N = 145)

Item	Response	%
1. Have you ever recommended that a family consider the option of cochlear implantation?	Yes	92
	No	8
2. Was the topic of cochlear implants part of your educational training?	Yes	45
	No	51
3. At what point in your audiological management of a child with a profound bilateral sensorineural hearing loss do you first discuss cochlear implants?	At time of diagnosis	23
	During hearing aid evaluation	3
	After aided audiological results	25
	Other (or multiple responses)	48
4. If a specific age were not a criterion for cochlear implantation, what is the earliest age you feel you could refer a child for a cochlear implant?	3 to 6 months	8
	7 to 12 months	21
	13 to 18 months	39
	19 to 24 months	28
	(Other or multiple responses)	4
5. If a child has a profound hearing loss as a result of meningitis, at what point would you mention the topic of cochlear implants to the family?	At time of diagnosis	54
	During hearing aid evaluation	3
	After aided audiological results	18
	Other (or multiple responses)	24
5a. Would your recommendations differ if the child were prelingual rather than postlingual?	Yes	40
	No	56
6. Do you feel comfortable recommending or discussing cochlear implants with families?	Yes	83
	No	14
7. Does your facility have a cochlear implant program?	Yes	62
	No	38
7a. If yes, are you part of the cochlear implant team?	Yes	27
	No (or no program)	73

In spite of these responses indicating a favorable attitude toward cochlear implants and early implantation, there may be reluctance to aggressively pursue implantation. Only 23% of the respondents consistently discuss the option of implantation at the time of diagnosis of a profound hearing impairment, with another 25% waiting until aided audiological information is obtained (item 3). However, nearly half of the respondents — 48% — indicated “other” or checked multiple responses. Among individuals checking multiple responses, some indicated they would discuss implants at the time of diagnosis only if the parents raised the issue. A common written response suggested that discussion of cochlear implants is based on the families’ reaction to the initial diagnosis that their child has a profound hearing impairment. Others reported that regardless of results on the aided audiological information, they felt that the child should utilize amplification for 6 months to 1 year before they recommended implants to the family. Another comment revealed that some audiologists did not mention the implant to families because they were afraid that the family would not complete a trial with conventional hearing aids.

An additional aspect to consider was management of a child who acquired hearing loss as a result of meningitis (item 5). A dramatic increase — to 54% — was noted in

the number of respondents who mention the topic of cochlear implants at the time of diagnosis. In addition, it made little difference whether the child’s hearing loss occurred prelingually or postlingually.

DISCUSSION

The responses to this survey suggest a certain ambivalence on the part of pediatric audiologists. The value of early implantation seems to be accepted, and yet the great majority of respondents do not consistently prepare families for this possibility by discussing implantation at the earliest opportunity. We encourage pediatric audiology departments to establish a policy on counseling parents about cochlear implants. We realize that every situation is different and every audiologist has his or her own views on management of a family and patient. However, if we are to truly empower parents to make decisions for their children, we must give them all of the information. We believe that if the topic of implants is proposed not as a cure but as another option, parents will have the additional information that may be needed to aid them in the decisions they will face with a child’s newly diagnosed deafness.

ACKNOWLEDGMENT — We thank the pediatric audiologists who participated in the survey.

STRUCTURAL ANALYSIS OF NARRATIVES PRODUCED BY A GROUP OF YOUNG COCHLEAR IMPLANT USERS

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The development of the narrative genre is of special interest in deaf children as almost all teacher instruction and written materials are presented in language beyond the sentence level. Narrative skills are critical for successful school achievement and have been found to be quite predictive of later academic success in groups of normal-hearing (NH) children.¹⁻³ Little is known about profoundly deaf children's narrative production skills. With the advent of the cochlear implant, it has become increasingly important to assess deaf children's discourse ability. Access to auditory information via a cochlear implant, especially if initiated at an early age, may decrease the time required for special education and result in an earlier entry into a mainstream education setting. The need to assess deaf children's narrative ability is critical if it is found to impact academic achievement as in the case of hearing children.

In this study, narratives elicited from a group of profoundly deaf children who used cochlear implants and a group of NH children of similar age were analyzed to 1) identify whether auditory speech perception ability associated with cochlear implant use is related to narrative production performance, 2) evaluate the relationship between narrative production and reading ability, 3) investigate the differences in narrative productions between orally educated deaf children and those who have been educated in simultaneous communication (SC) programs, and 4) compare and contrast the narratives produced by deaf children with those of age-matched NH peers. It was hypothesized that children with improved speech perception resulting from implantation and children who depended on oral communication would produce narratives more closely approaching those of their NH age-mates. These improved narrative abilities should also be associated with higher reading levels.

METHODS

Subjects. A sample of 43 prelingually profoundly deaf children between the ages of 8 years and 9 years 11 months (mean age, 9 years 1 month) were evaluated. Twenty-two used oral communication, and 21 SC, as their primary mode of communication. All the children had at least 4 years of cochlear implant experience and normal nonverbal IQs. Seventy percent were mainstreamed for at least part of the day. A group of 28 NH children between 8 years and 9 years 11 months served as the control group. These children were recruited from 2 local private schools and identified by their teachers as having no speech or language problems and as progressing well academically.

Narrative Production Task. The children were required to narrate events that occurred in an 8-picture story sequence in their preferred mode of communication. The

narrative productions were transcribed from videotape for the deaf children and from audiotape for the NH children.

The following additional measures were obtained from the cochlear implant users: 1) Test of Auditory Comprehension of Language-Revised (TACL-R),⁴ administered individually in simultaneous communication; 2) Peabody Individual Achievement Test-Revised (PIAT-R),⁵ with sections on reading recognition and reading comprehension; 3) Word Intelligibility by Picture Identification (WIPI)⁶; 4) Lexical Neighborhood Test (LNT)⁷; and 5) Bamford-Kowal-Bench (BKB) Sentences.⁸

Coding System. Each narrative was divided into clauses that were coded with the use of a modified version of the high point analysis.⁹ Types of narrative structures included *orientations* (clauses that provide the setting of the narrative, formalized beginnings and codas), *complicating actions* (narrative clauses that refer to a chronologically ordered event), *evaluations* (clauses that provide the point of the narrative), and *resolutions* (clauses that occur after the high point, resolving the action). In addition, the use of the following conjunctions was coded: coordinating (*and*, temporal (*and*, *then*, and *then*, *next*, *after*), causal (*because*, *so*, *if*), and other.

RESULTS

Narrative Structures. The average proportional use of each narrative structure type exhibited by the NH 8- and 9-year-olds was about 30% complicating actions, 30% evaluations, 20% orientations, and 20% resolutions. The 2 deaf samples differed from this pattern in the following ways: 1) the SC group used significantly more orientations (mean, 36%; $F(1,47) = 6.73$, $p < .01$), and 2) both the SC and oral groups used significantly fewer resolutions (SC mean, 11%; oral mean, 13%; $F(1,47) = 9.3$, $p < .01$ and $F(1,48) = 4.41$, $p < .05$).

Conjunction Analysis. No significant difference was obtained among the 3 groups in the use of coordinating *and*. Analysis of variance revealed a significant difference in the use of temporal conjunctions between the NH group and each deaf group (NH mean, 42%; oral mean, 26%; SC mean, 24%; $F(1,48) = 7.22$, $F(1,47) = 8.28$; $p < .01$, respectively). The SC group was found to use significantly fewer causal conjunctions than the NH group (NH mean, 15%; SC mean, 4%; $F(1,47) = 14.3$, $p < .01$). Analysis of variance revealed a significant communication mode effect for the use of causal conjunctions to link semantic relations (oral mean, 12%; SC mean, 8%; $F(1,41) = 5.18$, $p < .05$). Oral children produced significantly more causal conjunctions in their narratives. The NH group used significantly more conjunctions in their narratives than the oral and SC groups (NH mean, 68%; oral mean, 48%; SC

TABLE 1. CORRELATIONS BETWEEN SPEECH PERCEPTION ABILITY AND NARRATIVE STRUCTURES AND CONJUNCTIONS

	WIPI	LNT	BKB Sentences
Orientations	-.62	-.51	-.5
Evaluations	.50	.48	.41
And	.50	.47	.46
Causal conjunctions	.56	.55	.57
Total use of conjunctions	.60	.53	.61

All correlations were significant at $p < .01$.

mean, 31%; $F(1,48) = 8.97$, and $F(1,47) = 25.11$; $p < .01$, respectively).

Relationship Between Narrative Performance and Speech Perception, Language, and Reading Ability. The correlations between selected structures and conjunctions with speech perception scores are shown in Table 1. These correlations suggest that those children who received more benefit from their cochlear implants used fewer orientations and more evaluations and were more likely to recruit conjunctions to link semantic relations in their narratives. The correlations with reading test scores are shown in Table 2. Better readers were less likely to use orientations and more likely to use evaluations and conjunctions to link semantic relations. No significant correlations were obtained between any of the subtests of the TACL-R and narrative structures and conjunctions. These results indicate that scores reflecting a more normally structured narrative were not associated with scores reflecting greater language comprehension.

CONCLUSIONS

The narratives of deaf children from both oral and SC programs differed substantially from those of NH children. To the extent that the cochlear implant improved speech perception, it appeared to have a positive impact on narrative production. Better speech perceivers produced narratives that were more similar to those of their NH age-mates. Narrative production was associated with academic achievement in that better readers were more

TABLE 2. CORRELATIONS BETWEEN READING ABILITY AND NARRATIVE STRUCTURES AND CONJUNCTIONS

	Reading Recognition	Reading Comprehension
Orientations	-.48*	-.40*
Evaluations	.45*	.32†
Causal conjunctions	.45*	.33†
Total use of conjunctions	.53*	.46*

* $p < .01$.

† $p < .03$.

likely to use fewer orientations, more evaluations, and more conjunctions in their narrative productions. This pattern more closely approximated the narratives of the NH group. None of the narrative measures correlated with the TACL-R. This finding underscores the importance of measuring beyond the sentence level in the assessment of children with language learning difficulties.

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VOWEL PRODUCTION IN CHILDREN USING COCHLEAR IMPLANTS

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In the 10 years since children were first fitted with cochlear implants, many researchers have documented improvement in speech production abilities in these children compared with performance in children with hearing aids and tactile aids.^{1,2} Gains in speech production have also been documented to occur over time with use of the device.³⁻⁵

However, in more than 100 children fitted with implants

at the University of Iowa Hospitals and Clinics, there has been considerable variability in speech perception and production outcomes. Other researchers have also noted great variability in the speech production skills of children with cochlear implants.^{6,7} On the basis of 4 years of experience with the device, 3 broad trends of performance were identified. Children were grouped in these categories, labeled A, B, and C, on the basis of their speech production and perception skills.⁸ The children in group A tend to

VOWEL PRODUCTION RESULTS REPORTED IN PERCENTAGES FOR THREE DIFFERENT OUTCOME GROUPS OF CHILDREN USING COCHLEAR IMPLANTS

	Time of Visit	C	C + GA	E
Group A	Preimplant	16	16	84
	12 mo	33	33	67
	24 mo	41	41	59
	36 mo	37	37	63
	48 mo	51	51	49
Group B	Preimplant	21	60	40
	12 mo	24	33	67
	24 mo	41	50	50
	36 mo	51	69	31
	48 mo	53	63	36
Group C	Preimplant	23	77	23
	12 mo	45	63	37
	24 mo	64	77	23
	36 mo	75	87	13
	48 mo	75	89	11

C — correct production; C + GA — correct and good approximation; E — error.

demonstrate limited speech perception skills and poor speech intelligibility (<39% phonemes correct). The children in group B exhibit moderate skills in speech perception and speech production (40% to 69% phonemes correct). The children in group C typically are able to identify words in open-set speech recognition tasks. In terms of speech production, the children included in group C are highly intelligible (70% to 100% phonemes correct) in spontaneous speech.

This project was initiated to analyze the speech errors of children with implants in an attempt to account for the great variability of performance seen across children and, more important, to predict which children will more easily gain speech skills and which children will need extensive help in an attempt to acquire those skills.

METHODS

Twelve children were included in this preliminary study. Four children (2 boys and 2 girls) in each speech outcome group were included. All of the children received Nucleus 22-channel cochlear implants at an average age of 4 years 4 months. None of the children showed evidence of surgical complications that would be indicative of possible poor performance with the device. All participants came from middle-class families with English as the only language spoken in the home. A manual code for English was also used by the families for communication. The parents' signing skills were not evaluated as part of this study. The causes of deafness for the group included meningitis (2 children), cytomegalovirus (1), Waardenberg syndrome (1), connexin 26 nonsyndromic recessive deafness (1), and unknown (7). All of the children received annual checks of their device and fine-tuning of their individual processor settings. All the children were educated in the Iowa public schools with a simultaneous communication approach. The individual program goals and frequency of services were determined at the local level, and these services were reviewed annually. Suggestions for therapy were provided by the implant team.

Each child was videotaped before implantation and at annual follow-up appointments through the 48-month postimplantation evaluation. Speech data were obtained from a story re-tell task. The first 50 words of the speech sample were used. First, each sample for each age interval was analyzed with Reduced Aspect Feature Transcription (RAFT).^{9,10} The RAFT procedure includes the coding of vowel tokens on the basis of height and place features. In addition, the closest identifiable International Phonetic Alphabet symbol was identified for each vowel produced in order to evaluate the approximation of the vowel production to that of the target word. Each production was classified as correct, a good approximation, or an error. A good approximation was defined as a vowel made in the correct place in the mouth (front, middle, or back) and only in error by 1 height position.

RESULTS

In terms of the number of vowel tokens produced, the children in group A averaged 5 vowel tokens, compared with 40 vowel tokens for groups B and C before implantation. On percentage correct productions of vowels, the children in group A also showed a severely limited use of their oral cavity and control of their vowel productions, even with 4 years of experience with their devices. The children in group C demonstrated a rapid growth in vowel accuracy, distinctly different from that of the other groups, 12 months after implantation. Group B differed from group A children in that the children in group B showed slow and steady improvement in vowel production over time. The Table shows the accuracy of vowel productions over time for the 3 groups of children.

CONCLUSIONS

The results of this preliminary study suggest that detailed analysis of children's speech before implantation and in the first 2 years after implantation can reveal patterns of speech acquisition that could be used as prognostic indicators of speech development. The data suggested that children who became proficient speakers quickly made gains in vowel production and continued to improve in this area over time. Their errors in vowel production were more likely to be good approximations of the vowel target than those of the children who did not become proficient talkers. Although not part of this study, the skills of the local therapist and the family are important factors in the success of children with cochlear implants. Unfortunately, these factors could not be controlled in this study, but they warrant further investigation. In addition, the therapy approaches used with the highly intelligible children should be investigated. Most important, further research is needed to verify these initial findings and to determine whether children with poor speech production can be helped with intensive treatment, when the best time is to intervene, and what types of therapy procedures and feedback are most appropriate.

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COMPARISON OF LANGUAGE ABILITY IN CHILDREN WITH COCHLEAR IMPLANTS PLACED IN ORAL AND TOTAL COMMUNICATION EDUCATIONAL SETTINGS

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INTRODUCTION

Previous research has demonstrated that children with cochlear implants placed in oral educational settings have significantly better speech perception abilities than those in total communication environments.¹ However, one important goal of pediatric implantation is linguistic development, and speech perception ability does not necessarily reflect this. This study examines and compares the linguistic abilities of young implant recipients in oral and total communication settings.

METHODS

The test battery comprised 4 standardized language assessments: the Peabody Picture Vocabulary Test-III (PPVT-III),² the Expressive Vocabulary Test (EVT),³ the Test for Auditory Comprehension of Language-Revised (TACL-R),⁴ and the Grammatical Analysis of Elicited Language (GAEL).^{5,6} The PPVT-III and the TACL-R are tests of receptive language, and the EVT and GAEL assess expressive language. Testing was performed in the communication mode preferred by the child; therefore those children in oral settings were tested using only speech, and children using total communication were examined using a combination of speech, signed English, and finger-spelling.

Most testing was performed at the University of Miami by 2 experienced audiologists, both of whom had taken college-level courses in American Sign Language. However, certain test materials are invalid if administered more frequently than annually, so if children had recently undergone any of the tests at their own schools or therapy centers, these results were utilized. A third person, who administered none of the tests and had very little prior

knowledge of the children's language abilities, performed all test scoring to ensure that no bias was introduced.

RESULTS

The patient group consisted of 24 children; their characteristics are displayed in Table 1. Twelve of these children receive education in total communication programs, all of which are located in public school systems. The remaining 12 are placed in public school oral programs (3 children) or receive auditory-verbal therapy in conjunction with mainstream school placement (9 children). All the children were prelingually deaf, except 1 child in the oral group, who was deafened at the age of 19 months after meningitis. The cause of deafness was unknown for most children in each group; other causes were meningitis, cytomegalovirus, Usher's syndrome, Mondini dysplasia, and rubella. The mean age at implantation is shown

TABLE 1. SUBJECT CHARACTERISTICS FOR ORAL AND TOTAL COMMUNICATION CHILDREN

	Oral (n = 12)	TC (n = 12)
Boys	4	7
Girls	8	5
Nucleus MSP	0	4
Nucleus Spectra 22	10	8
Clarion	2	0
Age at implantation (mo)	73 ± 27 (33-132)	81 ± 34 (31-135)
Length of implant use at time of PPVT-III test (mo)	38 ± 14 (15-58)	54 ± 16 (19-80)
Age at time of PPVT-III test (mo)	111 ± 17 (84-148)	136 ± 38 (76-197)
Single data (first 5 rows) are numbers of children. Last 3 rows are mean ± SD, with range in parentheses.		
TC — total communication.		

TABLE 2. LANGUAGE DELAY IN MONTHS FOR ORAL AND TOTAL COMMUNICATION CHILDREN

	Oral (n = 12)		TC (n = 12)		Statistical Test	p
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range		
EVT	21 $\pm$ 36	-89-47	56 $\pm$ 39	12-136	t-test	.032
PPVT-III	45 $\pm$ 19	16-65	61 $\pm$ 46	9-136	Mann-Whitney	.817
TACL-R	36 $\pm$ 20	-4-66	63 $\pm$ 39	22-133	Mann-Whitney	.175
GAEL prompted language quotient	86 $\pm$ 21	59-122	71 $\pm$ 25	36-110	t-test	.146
GAEL imitated language quotient	89 $\pm$ 18	54-112	73 $\pm$ 28	31-112	t-test	.110
PPVT-III standard score	65 $\pm$ 14	48-92	65 $\pm$ 21	40-96		
EVT standard score	79 $\pm$ 16	58-123	68 $\pm$ 18	40-93		

in Table 1. Data for the length of implant use and age at the time of testing are included for 1 test (PPVT-III); in some cases, the other tests were performed at slightly different times, and therefore the data are not identical.

The raw scores obtained were converted to age equivalents by use of the normative data available, and the chronological age at testing was compared to the test age equivalents, thus providing a measure of language delay. The TACL-R only provides normative data up to the age of 9 years 11 months, and 1 oral child and 1 total communication child exceeded this level. Nine of the children were tested with the GAEL-C, and the remaining 15 were tested with the GAEL-S. The GAEL provides normative data for normal-hearing and hearing-impaired children, but for this study, comparisons were made only with the normal-hearing data. The raw scores were converted to prompted and imitated language quotients, and all children's data were compared with normative data in the oldest age range: 4 years 6 months to 5 years for the GAEL-S, and 5 to 5 years 11 months for the GAEL-C. The parameters were examined with the F test; those with comparable variances ($p > .05$) were analyzed with the 2-tailed *t*-test, and for all others, the Mann-Whitney U test was used. The language test results are shown in Table 2. (Negative language delay values indicate a language age higher than the chronological age.) Mean results are not included for the TACL-R test, because most children scored the minimum score and were at or below the 1-percentile rank compared with normal-hearing children in their age group. Only 2 total communication children and 5 oral children scored above the minimum level.

The oral children demonstrated significantly less language delay than the total communication children on the EVT test. Although they also performed better on the PPVT-III, TACL-R, and GAEL, these differences were not statistically significant. There was no significant difference in the age at implantation between the 2 subject groups; however, the total communication children had been using their cochlear implants for significantly longer than the oral group when they were tested with the PPVT-III, EVT, and TACL-R. The GAEL testing on some of the total communication group had been completed previously at another facility, and there was not a statistically significant difference in the length of implant use at the time of this test.

The PPVT-III and EVT use the same normative population, and therefore their standard scores can be compared. The mean EVT standard score for the oral children

was significantly higher than their mean PPVT-III score (on *t*-test, $p = .0235$); there was no such difference for the total communication children (*t*-test, $p = .728$). This difference for the oral children still occurred when the results from 1 child who performed above her language age on the EVT were removed from the analysis. This finding suggests that the oral children are better at demonstrating their vocabulary knowledge in an open expressive format rather than a receptive format. It is unclear why this should be the case; perhaps speech perception testing of the oral children at the same time would have elucidated this matter.

There were too few children in the study for us to test the significance of any differences between children in oral programs and those in mainstream settings with auditory-verbal therapy.

CONCLUSIONS

Although the children in the total communication group had been using their cochlear implants for significantly more time than those in the oral group, the oral children performed significantly better than the total communication children on the EVT. The oral children also performed better on the PPVT-III, TACL-R, and GAEL, but these differences were not statistically significant. This study was a preliminary investigation into the language ability of children in different educational settings, using a small sample of children (12 in each group). It was not possible to assess the patient groups in terms of factors such as cognitive ability, family support, or amount of therapy received, but there is no reason to suspect that these would differ significantly. In addition, more detailed investigation into the reasons particular educational regimens were selected for individual children is required. It is possible that early indicators of language ability affected the selection of educational mode.

Further research is required, but these preliminary results suggest that the orally educated children had better language skills than did the children in total communication programs.

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SPEECH INTELLIGIBILITY OF PRELINGUALLY DEAF CHILDREN WITH MULTICHANNEL COCHLEAR IMPLANTS

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INTRODUCTION

The most obvious benefit of a cochlear implant (CI) is aid in speech perception. However, one of the major benefits of CIs is in the development of intelligible speech, something that is very difficult for congenitally profoundly deaf children. Although the assessment of speech intelligibility by naive listeners (rather than by parents or clinicians) is laborious and time-consuming, this measure has high reliability and face validity. Previous studies have demonstrated substantial increases in intelligibility by profoundly deaf children after receiving CIs.^{1,2} These studies compared the intelligibility of CI users with intelligibility scores predicted for hearing aid (HA) users. Most subjects in the CI group were users of the multipeak (MPEAK) stimulation strategy rather than the state-of-the-art strategies spectral peak (SPEAK) or Continuous Interleaved Sampler (CIS). It was found that the CI users matched the speech intelligibility of HA users, with a pure tone average (PTA) between 100 and 110 dB hearing level (HL) after 1 to 2.5 years of CI use. However, the CI users did not reach the speech intelligibility shown by HA users with more residual hearing (90 to 100 dB HL), even after 5 years of CI use.

The present study expands earlier work by analyzing a new population of CI users that better represents the current demographics of pediatric cochlear implantation: children with profound prelingual hearing impairment who were fitted with implants before the age of 6 and who had used a state-of-the-art stimulation strategy (SPEAK or CIS) since initial stimulation. We hypothesized that the speech intelligibility of these children would match or exceed that of HA users, for 2 reasons. First, the new stimulation strategies have resulted in higher levels of speech perception and spoken word identification³ (Meyer and

Svirsky, this supplement, pp 49-51), which are prerequisites for the development of normal speech production. In addition, earlier implantation may provide some CI users with access to the ambient language well within the critical period presumed to be important for the development of a linguistic system.

METHODS

Participants Who Used HAs. This group of children was subdivided into 4 groups, according to communication mode (either oral communication [OC] or simultaneous communication [SC]) and residual hearing (PTA between 90 and 100 dB HL or between 100 and 110 dB HL). The mean age at onset of deafness and the age at initial HA fitting did not differ as a function of communication mode. The children were between 2 and 12 years of age at the time of testing.

Participants Who Used CIs. All 44 children had prelingual profound hearing losses and received a CI before the age of 6. With very few exceptions, the CI users had unaided PTAs of 110 dB HL or more in the better ear. Table 1 shows additional information about all groups of HA and CI users. Before implantation, the intelligibility of most CI users was zero.

Procedures. Each subject produced 10 sentences that were repeated after an examiner's spoken model. The children under 6 were administered 1 list from the Beginner's Intelligibility Test⁴ (BIT), in which an imitative response is elicited with the help of objects, pictures, and oral presentation. Older children (>6 years) who could read were given the Mønsen Sentences Test.⁵ The sentences were recorded on cassette tape, digitized, and later played back, in random order, to panels of 3 listeners with no experience in listening to deaf speech. The listening sessions

TABLE 1. AGES AT ONSET OF PROFOUND HEARING LOSS AND INITIAL FITTING WITH HEARING AID AND COCHLEAR IMPLANT

Communication Mode	Group	N	Age at Onset (y)	Age at HA Fitting (y)	Age at CI Fitting (y)
Oral	CI	23	0.3 ± 0.7	1.2 ± 0.6	3.1 ± 1.0
	HA90-100	11	0.2 ± 0.5	2.1 ± 1.3	
	HA100-110	18	0.3 ± 0.7	1.3 ± 0.7	
Simultaneous	CI	21	0.1 ± 0.4	1.6 ± 0.5	3.3 ± 1.0
	HA90-100	10	0.3 ± 0.8	1.4 ± 0.9	
	HA100-110	23	0.5 ± 0.8	1.3 ± 0.7	

Data are mean ± SD. See text for abbreviations.

TABLE 2. LINEAR REGRESSION OF INTELLIGIBILITY AS FUNCTION OF AGE FOR DIFFERENT GROUPS OF HEARING AID USERS

Group	Mode	Slope (%/y)	Intercept (%)	r	p	N
HA90-100	OC	7.6	-6.6	+81	<.001	28
HA90-100	SC	10.4	-46.0	+88	<.001	21
HA100-110	OC	7.8	-29.0	+85	<.001	30
HA100-110	SC	0.9	3.9	+15	NS	47

Second and third columns show results of linear regressions of intelligibility scores as function of age at testing, for each group of HA users indicated in first column. Two rightmost columns show correlation between intelligibility and age at testing for each group, significance of correlation, and number of data points for each group. See text for abbreviations.

were conducted in a double-blind fashion; neither the listeners nor the experimenters knew whether the children in the tape being played were HA or CI users. The outcome measure was the average number of key words correctly transcribed by the listeners. The CI subjects were tested just before initial hookup and at 6-month intervals thereafter, although some subjects were not available at all intervals. The HA subjects were tested between 1 and 4 times.

Data Analysis. Linear regressions of intelligibility as a function of age at testing were conducted for each of the 4 HA groups (users of SC or OC in the HA90-100 or the HA100-110 groups). The resulting regression lines were used to obtain predicted intelligibility scores for each HA group at a given age. The intelligibility scores for the CI users at a given interval were compared with the scores predicted for each HA group at the corresponding age. Comparisons between observed scores for CI users and predicted scores for HA users were carried out separately for users of SC and OC.

RESULTS

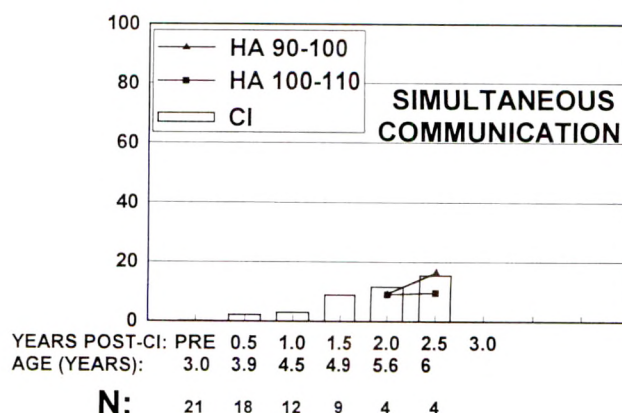
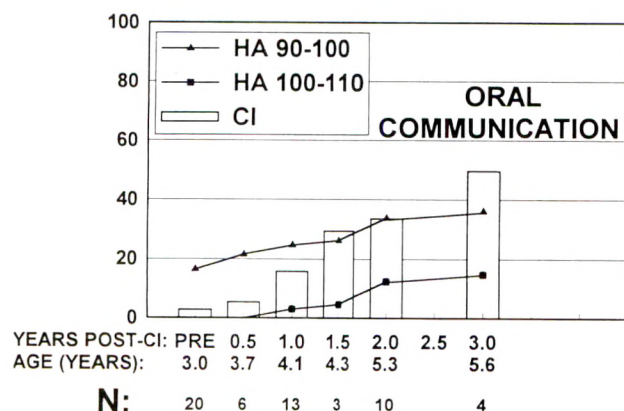
Table 2 shows the results from the regression analyses. Three of the 4 subgroups (users of OC in the HA90-100 and HA100-110 groups, and users of SC in the HA90-100 group) showed statistically significant correlations between intelligibility and age at testing. The rates of increase in intelligibility as a function of age were between 7.6% per year and 10.4% per year for these 3 groups and only 0.9% per

year for the users of SC in the HA100-110 group.

The bars in the Figure show the mean intelligibility scores for the CI users as a function of time after initial stimulation, for the CI users employing OC (top panel) or SC (bottom panel). The black symbols show the predicted intelligibility levels for the HA users of the same age as the CI users and the PTAs between 90 and 100 dB HL (triangles) or 100 and 110 dB HL (squares). These projections for the HA users were based on the linear regressions described above. Before implantation, the CI users showed intelligibility levels well below the predictions for either HA group. However, 1.5 to 2 years after implantation, both the SC and OC CI users reached the average intelligibility levels predicted for the HA90-100 group (ie, the level indicated by the bars at 1.5 to 2 years after implantation in the Figure is about the same as that indicated by the triangles). This happened because the average difference in intelligibility as a function of age at testing was about 6% per year for the SC CI users and about 16% per year for the OC CI users, enough to catch up with the more slowly developing HA subjects who used the same communication mode.

DISCUSSION

The main observation from the HA data is that intelligibility is highly correlated with age at testing for 3 of the 4 HA groups, suggesting that many profoundly deaf HA users become more intelligible over time, even without a CI, possibly as a result of both maturation and oral training. However, the differences in speech intelligibility as a function of implant use clearly exceed the changes over time predicted for profoundly deaf HA users on the basis of maturation and training, even for HA users with residual hearing in the 90- to 100-dB range. Before implantation, the intelligibility of the CI users in this study was close to zero. After 1.5 to 2.5 years of implant use, the speech intelligibility of the CI users was similar to the levels of speech intelligibility predicted for HA users with PTAs between 90 and 100 dB HL. Interestingly, the high levels of speech intelligibility by CI users with respect to HA users observed in this study are paralleled in studies of speech perception by CI and HA users³ (Meyer and



Comparison of average intelligibility measured in children with cochlear implants (CI) to average intelligibility predicted in hearing aid (HA) users of same age. Bars show average intelligibility as function of time after initial stimulation for CI users employing oral or simultaneous communication. Black symbols show predicted intelligibility levels for HA users of same age as CI users and with pure tone averages between 90 and 100 dB hearing level (triangles) or 100 and 110 dB hearing level (squares).

Svirsky, this supplement, pp 49-51). In conjunction with studies of speech perception and language development, speech intelligibility data may provide support for the future expansion of implantation eligibility criteria.

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